Advanced Macromolecular Engineering through Precision Polymerization with Alcohols as Key Reagents

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CONTENTS

GENERAL INTRODUCTION

Background

A Primary Structure of Polymers. The primary structure of polymers includes the following factors: (a) molecular weight, (b) molecular weight distribution, (c) tacticity, (d) terminal structure and (e) monomer sequence, and the control is mandatory for the expression of well-defined higher-order structures and excellent functions therewith (Figure 1). This is actually true for a natural polymer, typically DNA and proteins, which are of finely defined primary structures to induce their specific functions, namely, transcription of genome information, enzyme catalysis, and so on. On the other hand, it was impossible, or sometimes not attracted clear attention, to control of a primary structure in the synthetic polymers, and their applications were based on the inherent properties, (e.g., for plastics), irrelevant to their primary structures.

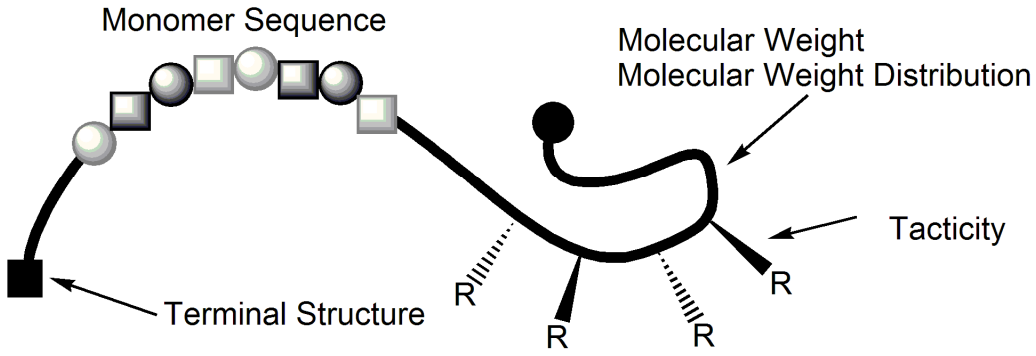


Figure 1. Primary structural factors on polymer chain

"Status Quo" in Precision Polymerization. On the contrary, recent progress in so-called "precision polymerization", typically "living polymerization" and "stereospecific polymerization", have opened the door to control the primary structure even for synthetic polymers, and allowed some advanced functions, e.g., thermoplasticity with triblock copolymers and crystalline property of isotactic poly(propylene). However, the precision in the structure is still inferior to natural polymers, and, more noteworthy is that simultaneous control over multiple factors is unachievable in some systems. Now, novel "macromolecular engineering" is required to control primary structure at will toward more advanced functions of polymeric materials.

		Primary Structure			
		Molecular Weight	Tacticity	Terminal Structure	Monomer Sequence
Propagating Species	Anionic	○	○	○	×
	Cationic	○	△	○	×
	Radical	○	△	△	×
	Coordination	○	○	○	×

○: Achieved, △: Partially Achieved, ×: Not Achieved

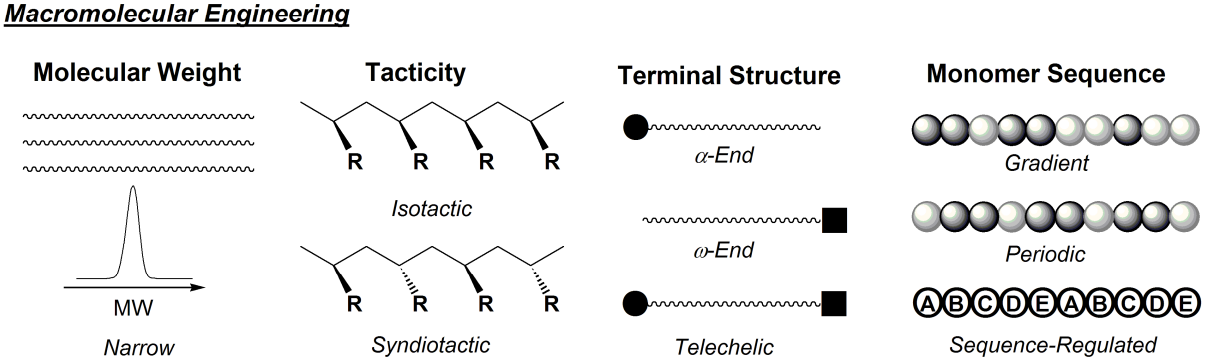


Figure 2. Status quo in precision polymerization

First, the author would like to describe the "status quo" in the four kinds of addition polymerizations (anionic, cationic, radical, and coordination) for the control of primary structure, i.e., molecular weight, tacticity, terminal structure, and monomer sequence to clarify the point at issue (Figure 2).

(a) Molecular Weight. Living polymerization[1-17] is now among the best method to control molecular weight of polymer. Therein, since the propagation reaction is not inhibited by unfavorable reactions such as irreversible chain transfer and termination reactions, active species (e.g., anionic, cationic, and radical) is "living" (long-lived) during the polymerization. Therefore, the molecular weight can be controlled by the feed ratio of a monomer to an initiator, and the molecular weight distribution becomes narrow. Since living polymerization system is generalized, now molecular weight control becomes possible in all the addition polymerizations including radical process.

(b) Tacticity. Tacticity, namely the specificity in configuration of main chain, imposes dramatic effects on the physical properties and functions of polymers. Thus, the control has been extensively explored in addition polymerizations. The pioneering example

is an isospecific polymerization of propylene with a heterogeneous Ziegler-Natta catalyst, and the produced isotactic poly(propylene) has been widely employed for materials by taking advantage of the crystalline propetry.[18] With this finding as a trigger, the coordination polymerization has been developed to control tacticity, and recently the catalyst evolution has been shifted to homogeneous catalysts (i.e., metallocene) for dual control over tacticity and molecular weight.[19-21] In anionic polymerizations, stereospecific polymerizations have been achieved in some systems through the molecular design for countercation or an additive to interact with the side group, and in most instances, molecular weight control is also possible (stereospecific living polymerization).[22] In contrast, tacticity control in radical polymerization is intrinsically difficult because of the absence of counterion, although certain bulky methacrylates[23] and methacrylamides[24] are known to polymerize stereospecifically due to the repulsion of the side group even via radical process. Recently, a more general method has been reported that utilizes the interaction of the pendent ester or amide in monomers and/or polymers with fluoroalcohol or Lewis acid.[25,26] However, the control degree is still below those by the coordination and anionic polymerizations.

In cationic polymerization, the tacticity control has been studied since early times, and, unexpectedly, the first stereospecific polymerization was studied with the cationic system. In 1947, Schildknecht produced the crystalline isotactic-rich poly(isobutyl vinyl ether) (PIBVE) with BF_3 catalyst at very low temperature[27] and then Vandenberg reported the isotactic-rich poly(alkyl vinyl ether) with heterogeneous catalyst (Vandenberg-type catalyst).[28] In addition to these classical researches, some stereospecific polymerizations have been developed in these years. For example, Ohgi et al. found that a BF_3-based catalyst gave highly isotactic polymer (*mm* = 79%; *m*: *meso* diad) in cationic polymerization of *tert*-butyl vinyl ether and the *mm* values were increased with the decrease of BF_3 complex size.[29] Ouchi et al. achieved a highly isospecific cationic polymerization of IBVE with a series of bisphenoxy titanium(IV) dichloride as a Lewis acid, coupled with the HCl adduct of IBVE as an initiator (*m* = 92%).[30] However, a higher level of tacticity control has never been achieved in cationic polymerizations, and more seriously, there is no effective way to control molecular weight and tacticity simultaneously.

(c) Terminal Structure. In principle, terminal structure can be controlled with living polymerization, and the functionalization for α-end is more accessible because the initiation is quantitative. On the other hand, ω-end functionalization is not necessarily easy,

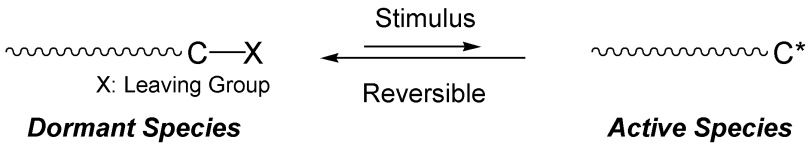
even though the terminal is living or active in living polymerization. Nevertheless, structural control for the ω-terminal is rather essential for a construction of more elaborate architectures, as demonstrated in living ionic polymerizations.[31,32] The difficulty in a modification of ω-terminal is more serious in living radical polymerization due to the neutral species. Indeed, there were limited reports on capping agents for living radical polymerization:[33-39] silyl enol ethers for ketones,[35] tin compounds for hydrogenation and allylation,[36,37] allyl compounds for hydroxy and epoxy groups,[37,38] and sodium azides for "click" reactions.[39] However, these methods seem to be either exotic, expensive, or inefficient, and so more feasible way with common reagents is required.

(d) Monomer Sequence. The most crucial disparity in the primary structure between synthetic and natural polymers comes from monomer sequence. For example, as for proteins, the sequence is perfectly controlled with 20 kinds of monomers via a transcription/expression process with an assistance of catalyst (enzyme). In contrast, in artificial polymerizations, the control of monomer sequence along one polymer backbone is still out of our reach. In radical copolymerization, for example, monomer sequence depends on monomer reactive ratios, and the resultant polymers are generally statistical copolymers, except for specific combinations that lead to alternating copolymers (e.g., styrene/maleimide[40]) and to gradient copolymers (e.g., styrene/acrylates[41]). On the other hand, fine sequence control in step polymerization is indeed possible by the Merrifield solid-phase peptide synthesis, though cumbersome procedures needed, e.g., repeated deprotection, condensation reaction, and product isolation.[42]

Now, sequence control attracts attentions even in addition polymerization,[43] since the individual propagation control has been gained for many kinds of monomers with living polymerizations. So far, some approaches have been reported to control the sequence on a polymer chain: 1) repetitive mono-addition of a monomer using a living polymerization system;[44] 2) sequential addition of functional monomers favoring cross-propagation into living polymerization;[45] 3) polymerization of monomers carrying programmed sequence in advance;[46,47] and 4) polymerization with a template-bearing initiator.[48] Although these methodologies have actually shown the possibility of the sequence regulation, they often include multi-step procedures, and more efficient strategy would be required accordingly.

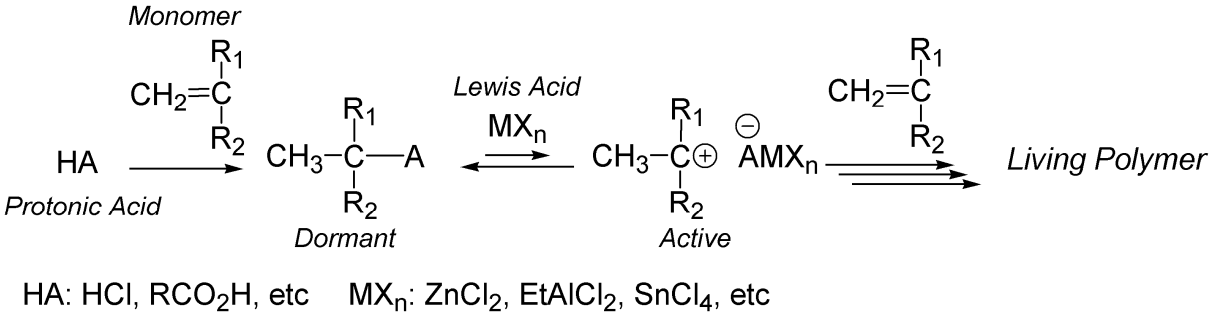
Thus, many subjects remain to be settled in the precision polymerization field. To achieve such advanced control, newly devised molecular design would be required. Here, as far as molecular weight control is presupposed, the design should be given on the basis of living polymerization. In the following section, a living polymerization with dormant species is described which is "base" system in this thesis.

Living Polymerization with Dormant Species. The concept of "living polymerization" was first proposed by Szwarc in 1956. He found that an anionic polymerization of styrene under rigorous condition free from water and oxygen gave well-defined polystyrenes of quite narrow molecular weight distributions.[2] After this breakthrough, similar polymerization control was achieved in other polymerizations,[1] even mediating more unstable growing species such as cationic,[3-12] radical.[13-17] The essential and general concept to achieve living polymerization is converting "active" species into "dormant" ones with a capping agent and reversibly activating the dormant species under some chemical or physical stimulus (Scheme 1). Thus, an instant concentration of active species is minute, leading to suppression of unfavorable side reactions, i.e., β-hydrogen elimination in cationic system and bimolecular termination in radical one. The concrete examples of the living polymerization with dormant species, i.e., "Lewis acid-catalyzed living cationic polymerization" and "transition metal-catalyzed living radical polymerization", will be described below.



Scheme 1. Dormant-Active Equilibrium

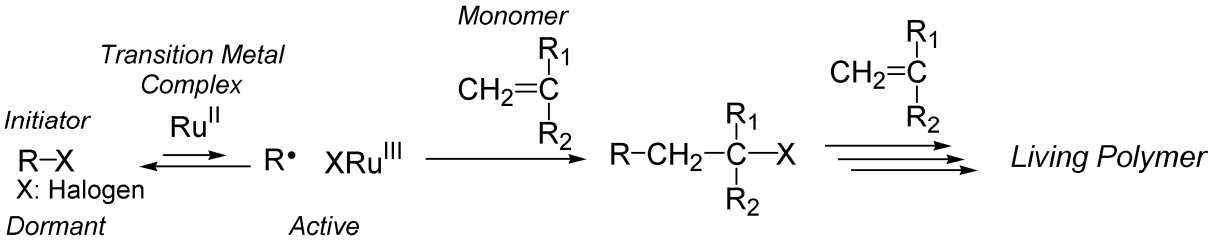
(a) Living Cationic Polymerization. In 1984, Higashimura and Sawamoto first accomplished living cationic polymerization of vinyl ether with HI/I_2 system. The system was later generalized as a "binary initiating system" consisting of a protonic acid (HA: initiator) and a Lewis acid (MX_n: activator). Here, the former adds onto the double bond of a monomer ($CH_2=CR_1R_2$) to form an adduct ($H–CH_2–CR_1R_2–A$), and then the given –C–A bond (dormant) is ionically (heterolytically) and reversibly activated by MX_n to generate a growing cation (active) accompanied by a counteranion (A^-MX_n; Scheme 2).[3] This system was then expanded for other monomers, i.e. isobutene[11] and styrene derivatives,[12] along with



Scheme 2. Lewis Acid-Catalyzed Living Cationic Polymerization

the development of various initiators (hydrogen halide, carbonic acid, benzoic acid, phosphoric acid etc.), activators/catalysts (I_2, $ZnCl_2$, $EtAlCl_2$, $SnCl_4$, $TiCl_4$, BCl_3, etc.), and additives (ether, ester, amine, sulfide, etc.).[3-10]

(b) Living Radical Polymerization. Because of the high reactivity or low stability of free radicals and their facile coupling and/or disproportionation reactions, a realization of the living radical polymerization had been considered impossible for a long time. However, the reversible activation concept allowed even living radical polymerization, after a decade of the discovery of the living cationic polymerization. In 1995, Sawamoto and Kamigaito first demonstrated molecular weight control in radical polymerization of methyl methacrylate (MMA) using CCl_4 and $[RuCl_2(PPh_3)_3]$, in conjunction with a bulky aluminum compound [$MeAl(ODBP)_2$, ODBP = 2,6-di-*tert*-butylphenoxy]. As with the cationic system (Scheme 2), a dormant carbon-halogen bond in the initiator or the polymer terminal is radically (homolytically) and reversibly activated into growing radical by the ruthenium catalyst via one electron redox ($Ru^{II} \leftrightarrow Ru^{III}$) (Scheme 3).[13] Soon after their discovery, a similar catalytic system with a Cu complex was reported by Matyjaszewski[15] and until now various transition metals (Ru, Cu, Fe, Ni, Mo, Mn, Os, Re, Co, Rh, and Pd) were employed for the control.[14-17]



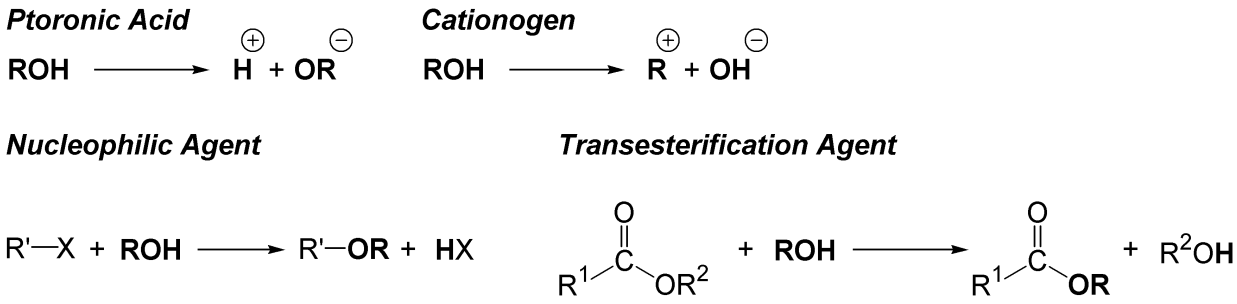
Scheme 3. Transition Metal-Catalyzed Living Radical Polymerization

Objectives

Given the above backgrounds, the author tackled three unachievable fields of precision polymerization (Figure 2) in this thesis:

(1) Control of "Tacticity" in Cationic Polymerization
(2) Control of "Terminal Structure" in Radical Polymerization
(3) Control of "Monomer Sequence" in Radical Polymerization

Upon these challenge, he focused on using "*alcohol*" as a key reagent. Alcohol (ROH) is very versatile and ubiquitously available compound. The oxygen atom of an alcohol polarizes both the O-H and the C-O bonds, and alcohol thus works both as a protonic acid (–OH) and as a cationogen (–C–O). Also, the lone electron-pair makes alcohol nucleophilic and esterification agents (Scheme 4). In sharp contrast to these potential versatilities as species and reagents, alcohols have not been employed so extensively in polymer synthesis so far, except for the usual uses as terminators (ionic polymerization), solvents (radical polymerization), and polymer precipitants. A key to the objectives is to turn conventional terminating and chain-transfer agents, or poisons, into more friendly and useful reagents to precisely control cationic and radical polymerizations.



Scheme 4. Various Roles of Alcohols

(1) Control of "Tacticity" with Alcohols as Initiators (Part I in Figure 3). In the first part of this thesis, the author employed alcohols as *initiators* in living cationic polymerization for the stereospecific polymerization. In cationic polymerization, alcohols have been conventionally known as powerful terminating and chain-transfer agents that convert cationic intermediates into the corresponding alkoxys, ω-olefins, etc.[3-10] In contrast, some hydroxyl compounds such as water adducts (H-CH_2-CHR-OH) of a vinyl monomer and

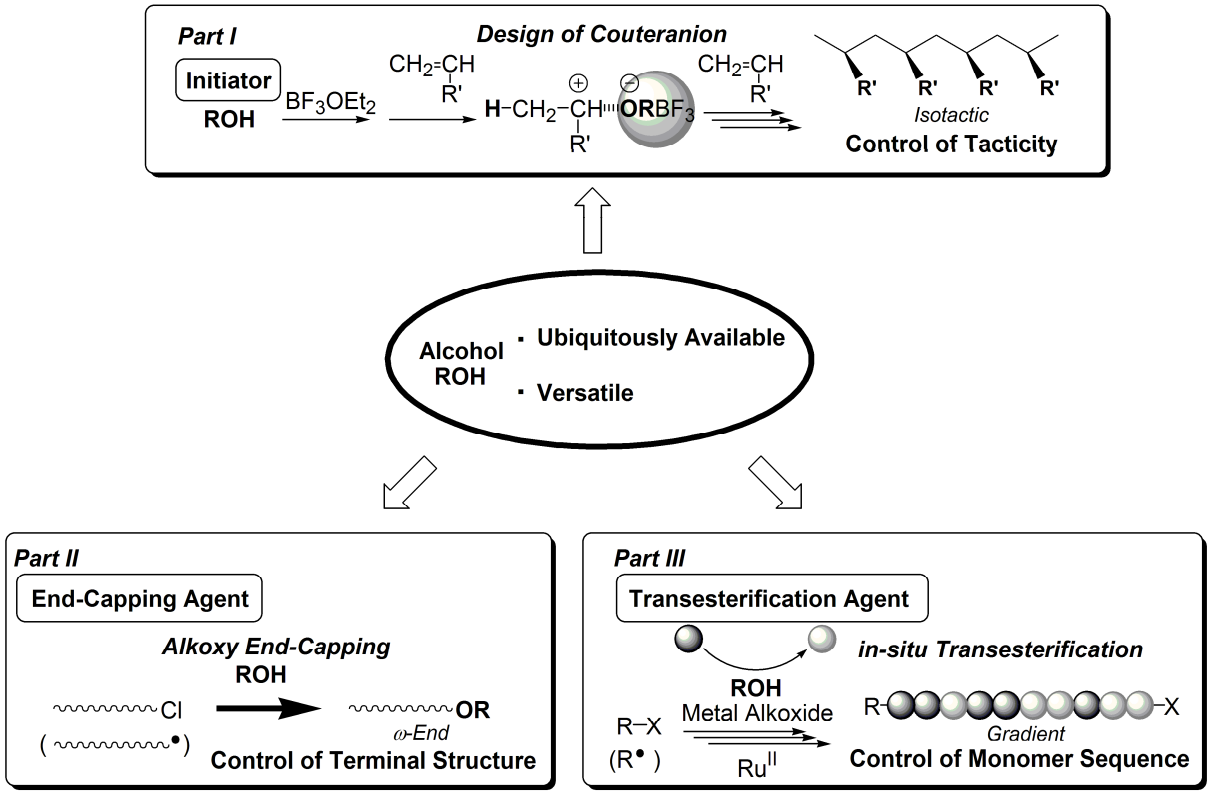
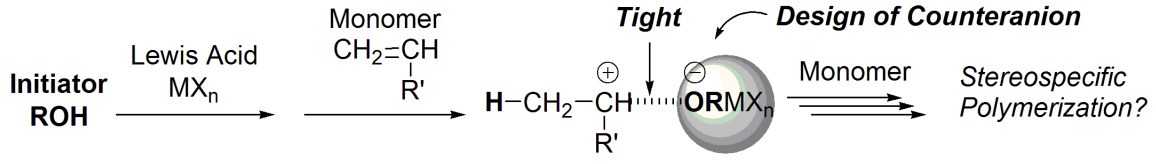


Figure 3. Precision polymerization with alcohols as key reagents

tertiary alcohols were reported to work as initiators for living/controlled cationic polymerization, where the OH^- counteranion associates with the cationic species.[49,50] These backgrounds indicate the possibility that even simple alcohols can work as initiators for living cationic polymerization. If alcohols (ROHs) can be used as initiators, the system is expected to control tacticity as well as molecular weight and molecular weight distribution of obtained polymers from the following reasons: (1) the ion pair between the alcohol-derived alkoxy counteranion (RO^-) and the growing cation might be tight because of its high nucleophilicity, and thus the direction of incoming monomer might become sensitive for the counteranion; (2) the structure and function of counteranions can be easily and systematically designed by changing alkyl groups (R) (Scheme 5).



Scheme 5. Design of Counteranion with Alcohols as Initiators

(2) Control of "Terminal Structure" with Alcohols as End-Capping Agents (Part II in Figure 3). For the second objective of this thesis, the author employed alcohols as *end-capping agents* in living radical polymerization for the end-functionalization. In metal-catalyzed living radical polymerization, there is no doubt that efficient, selective, and quantitative terminal transformation has long been required, in part to eliminate the terminal halogen that potentially induces undesired reactions upon polymer processing and, more importantly, to expand the versatility in polymer synthesis directed to, for example, block, graft, telechelic, and other functionalized macromolecules. However, the inherent stability of growing radical and terminal alkyl-halogen bonds renders end-functionalization relatively difficult. The author thus focused on the end-functionalization with alcohols through "umpolung" of the growing carbon-halogen bond via the addition of a "modifier monomer", such as *p*-methoxystyrene (pMOS) or α-methoxystyrene (αMOS), which carries a highly electron-donating as well as conjugating pendent group (Figure 4). Namely, this methodology consists of the following two steps: 1) the less reactive terminal carbon-halogen linkage is in-situ converted into an activated form by the radical addition of a modifier monomer; 2) the nucleophilic substitution with alcohols subsequently occurs for the umpoled carbon-halogen bond. Given a large variety of alcohols with additional functionality, the design of the alcohol quenchers will open a new route to replace the potentially noxious terminal halogen with a more useful terminal function.

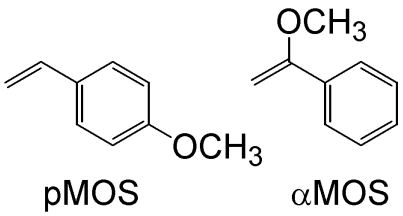


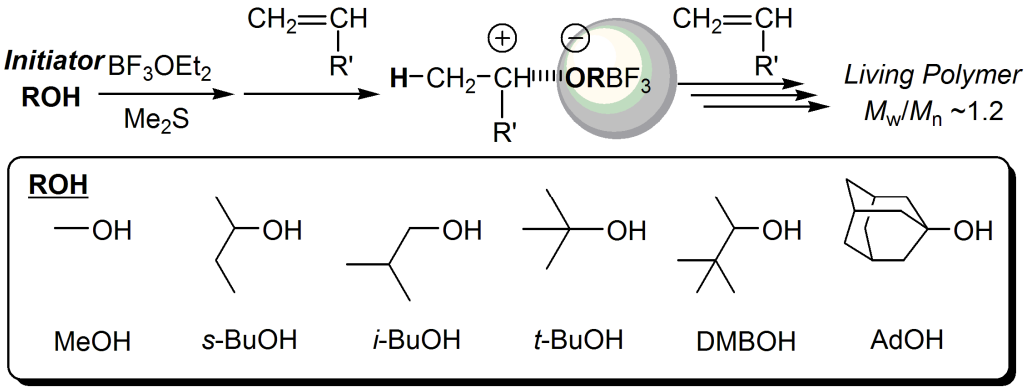
Figure 4. Modifier monomers

(3) Control of "Monomer Sequence" with Alcohols as Transesterification Agents (Part III in Figure 3). The final objective is to develop the more efficient and convenient method for the control of monomer sequence. To this end, the author employed alcohols as *transesterification agents* for a new tandem catalysis consisting of metal alkoxides-catalyzed transesterification of (meth)acrylates with alcohols and ruthenium-catalyzed living radical polymerization of the original and the in-situ formed comonomers. In addition to the use of alcohols, important is the intriguing dual roles of metal alkoxides as a catalyst for transesterification of esters and as a cocatalyst for living radical polymerization. The sequence control was examined from the point of view of the following factors: the structural effects of metal alkoxide cocatalysts and monomers, the concentration of cocatalysts and alcohols, reaction temperature, and, above all, the synchronization of the two reactions.

Outline of This Study

The present thesis consists of three parts: **Part I** (Chapter 1-2) deals with the control of tacticity in living cationic polymerization, where the counteranions accompanied by growing carbocations are designed with alcohols as initiators. **Part II** (Chapter 3-4) focuses on the end-functionalization with alcohols in metal-catalyzed living radical polymerization. The key is the "umpolung" of terminal carbon-halogen bond with a modifier monomer to be acceptable for a nucleophilic substitution with a variety of alcohols. **Part III** (Chapter 5-6) describes the tandem catalysis of transition metal-catalyzed living radical polymerization and metal alkoxide-catalyzed transesterification with alcohols as the efficient and convenient method for the sequence-regulated polymers.

Chapter 1 describes the antithetic function of alcohol in living cationic polymerization (Scheme 6). While conventionally terminators or chain-transfer agents, alcohols turned out to be surprisingly effective initiators for living cationic polymerization of vinyl ethers and *p*-methoxystyrene, coupled with borontrifluoride etherate (BF_3OEt_2) as an activator and dimethyl sulfide (Me_2S) as a basic additive. The polymerization with various alcohols gave polymers with molecular weights that increased in direct proportion to monomer conversion and agreed well with the calculated values, assuming that one alcohol molecule generated one polymer chain, with narrow distributions ($M_w/M_n \sim 1.2$). These results would open a way to design the structure and functions of the counteranion via a wide variety of ubiquitously available alcohols.

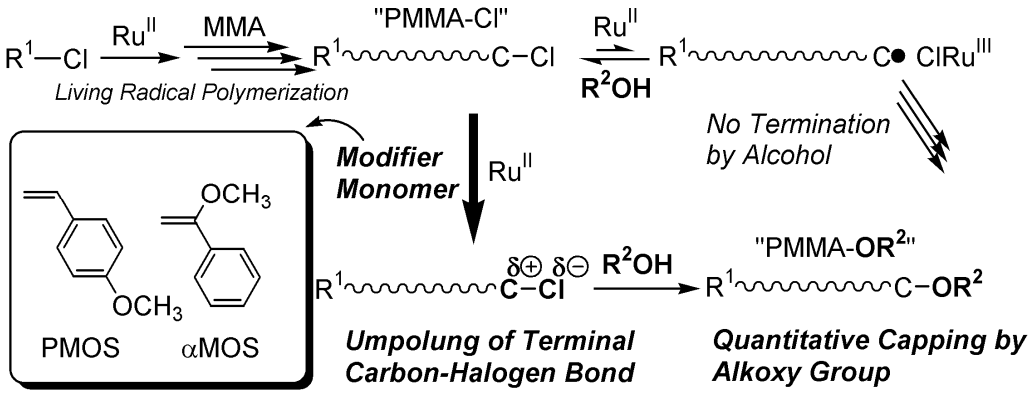


Scheme 6. Antithetic Function of Alcohol in Living Cationic Polymerization

Chapter 2 discusses the control of tacticity in living cationic polymerization of *tert*-butyl vinyl ether via a design of counteranion with alcohols as initiators. Various

alcohols were employed as initiators in conjunction with borontrifluoride etherate (BF_3OEt_2) as an activator and sulfides as a basic additive, and the tacticity of polymers obtained were analyzed by ^{13}C NMR. The isotacticity (*mm*) was indeed affected by the employed initiators, and generally bulky alcohols such as fluorenol gave high *mm* values (*mm* = 64%). Phenols were also applicable to this system and it turned out that their acidities (pK_a) made an effect on tacticity. Namely, the *mm* values increased with the decrease of pK_a. Additionally, the control of tacticity was also examined with the design of sulfide, where the sulfides containing alcohol moiety produced the isotactic-rich polymer (*mm* = 68%) with relatively narrow molecular weight distribution.

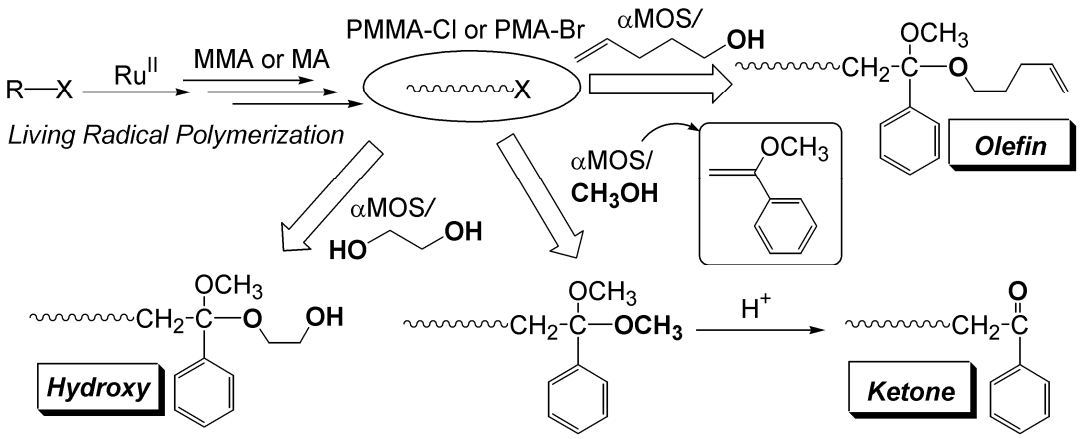
Chapter 3 focuses on the terminal "umpolung" for the quantitative alkoxy end-capping in metal-catalyzed living radical polymerization (Scheme 7). The crucial point was modification of the terminal carbon-halogen bond to be polarized for an acceptance of an ionic substitution by alcohol, which was brought about by attaching a modifier monomer with conjugated and electron-donating substituents, such as *p*-methoxystyrene (pMOS) and *α*-methoxystyrene (αMOS). Typically, the unreactive C-Cl terminal of poly(methyl methacrylate) (PMMA) obtained by ruthenium catalysis was quantitatively converted into PMMA-αMOS-OCH_3 with αMOS and methanol, which was analyzed with size-exclusion chromatography, NMR, and MALDI-TOF-MS. This method can be applied for the synthesis of various end-functionalized polymers with use of the corresponding alcohols.



Scheme 7. Terminal Umpolung of Terminal Carbon-Halogen Bond

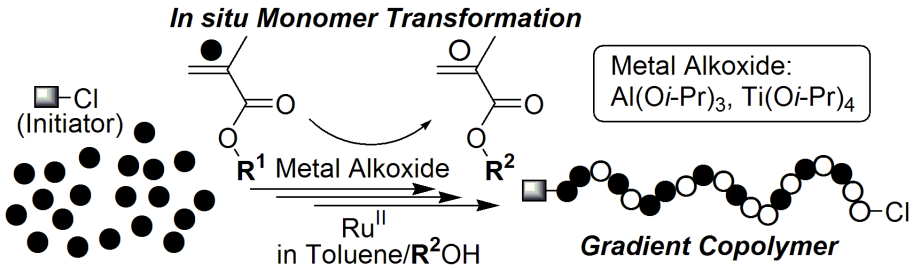
Chapter 4 deals with the end-functionalization with alcohols in metal-catalyzed living radical polymerization through "umpolung" of growing carbon-halogen bond (Scheme 8). This method consists of two steps: terminal umpolung with an addition of modifier monomers and the subsequent end-capping with alcohol. First, various monomers were examined as

potential modifier monomers to conclude that the modifier monomer should be bulky (geminally disubstituted) to inhibit the homopropagation and be electron-rich and conjugated for promoting the subsequent electrophilic substitution. In the second step, the alkoxy end-capping with a variety of functionalized alcohols, e.g. 4-penten-1-ol and ethylene glycol, produced the polymers with end-functional group such as a non-conjugated olefin and a hydroxy group; the simple methoxy from methanol may further be reduced into a more versatile ketone functionality. Similarly, telechelic polymers were also obtained from α,ω-bifunctional polymers.



Scheme 8. End-Functionalization with Alcohols through Umpolung

Chapter 5 presents the concurrent tandem living radical polymerization, where metal alkoxide-catalyzed transesterification with various alcohols and transition metal-catalyzed copolymerization were synchronized with each other (Scheme 9). Typically, a simple methyl methacrylate (MMA) was polymerized with a ruthenium catalyst in the presence of excess ethanol (EtOH) and Al(O*i*-Pr)$_3$ to produce gradient copolymers from MMA to ethyl methacrylate (EMA) along one polymer chain, where the original MMA was in-situ converted into EMA by the EtOH and Al(O*i*-Pr)$_3$ to vary the monomer composition during copolymerization. This concurrent tandem polymerization, in conjunction with a wide variety of alcohols, efficiently, conveniently, and in one pot produced various gradient copolymers including long alkyl chain and PEG pendent groups. The obtained copolymers further exhibited unique physical properties different from the corresponding random and block counterparts.



Scheme 9. Concurrent Tandem Living Radical Polymerization

Chapter 6 is directed toward the development of the efficient and convenient method for the control of monomer sequence by versatile tandem catalysis which consists of metal alkoxide-catalyzed transesterification of methacrylates with alcohols and ruthenium-catalyzed living radical polymerization of their monomers (Figure 5). The concurrent tandem catalysis efficiently produced various gradient copolymers, where the monomer sequence in gradient copolymers was controlled by species and/or concentrations of metal alkoxides and alcohols, and the reaction temperature. Monomer-selective or iterative transesterification gave random-gradient copolymers or gradient-block counterparts, respectively. This tandem catalysis had applicability to the synthesis of random or block copolymers by sequential tandem catalysis. This tandem system would open new door to prepare sequence-controlled copolymers efficiently and conveniently.

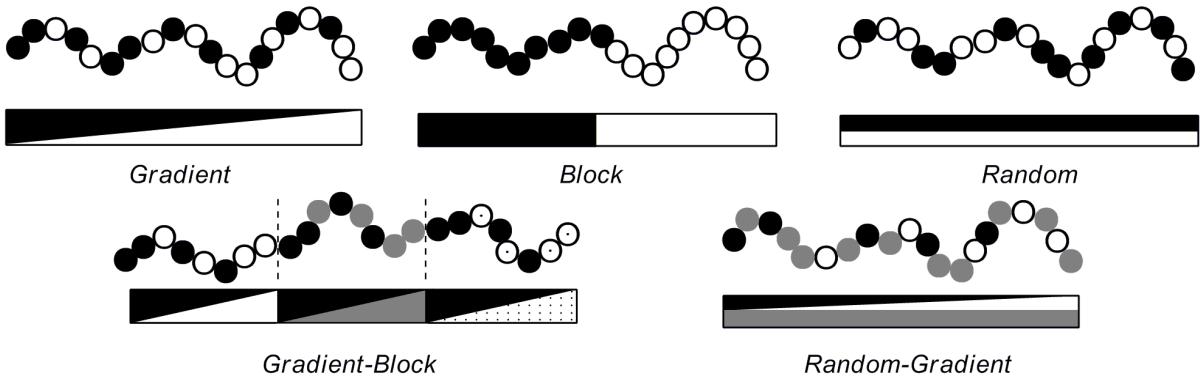


Figure 5. Sequence-controlled copolymers

In conclusion, this thesis presents advanced macromolecular engineering through precision polymerization with alcohols as key reagents to control primary structure such as tacticity, terminal structure and monomer sequence in addition to molecular weight and molecular weight distribution. The author hopes that this thesis contributes to further developments in precision polymerization.

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PART I

Control of Tacticity

Chapter 1

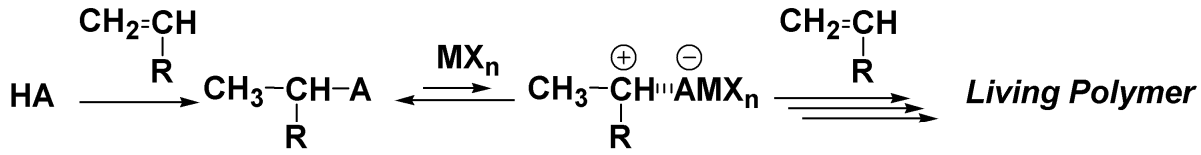
Alcohols as Initiators in Living Cationic Polymerization: From Terminator/Inhibitor to Useful Initiator

Abstract

Alcohols were employed as initiators for living cationic polymerization of vinyl ethers and *p*-methoxystyrene, coupled with tolerant Lewis acid, borontrifluoride etherate (BF_3OEt_2), although they were known to be poisonous reagent to bring about chain-breaking such as chain transfer/termination rather than such beneficial one for propagation and polymerization-control. As well known, without assistance of additive, ill-defined polymers with broad molecular weight distributions (MWDs) were produced. Even addition of conventional oxygen-based bases, e.g., ethyl acetate (AcOEt), 1,4-dioxane (DO), tetrahydrofran (THF), and diethyl ether (Et_2O) was less efficient in this system to control molecular weights and MWDs ($M_w/M_n > 2.0$). In contrast, by addition of dimethyl sulfide (Me_2S), MWDs of the resultant polymers became much narrower ($M_w/M_n < 1.23$) and the number-average molecular weight (M_n) increased in direct proportion to monomer conversion in agreement with the calculated values assuming that one alcohol molecule generates one polymer chain. Studying changed feed-ratio of alcohol to monomer and structural analyses with NMR and MALDI-TOF-MS indicated that quantitative initiation from alcohol giving alkoxide counteranion. This system opens a new way to employ a variety of alcohols as initiators, which would allow us to design variety of structures and functions of counteranion.

Introduction

In conventional cationic polymerization of vinyl monomers, the propagating carbocations are so unstable that they tend to undergo side reactions such as chain-transfer reactions, mainly caused by β-proton elimination, and irreversible termination. In contrast to this long-standing notion, Higashimura, Sawamoto and co-workers have developed living cationic polymerizations that allows suppression of such undesirable reactions and, in turn, precise control of molecular weights, molecular weight distribution and terminal groups of produced polymers.[1] Typical initiating systems for these living processes consist of a protonic acid (HA; A = halogen, CH_3COO, etc.) or its adduct with a monomer (H-CH_2-CHR-A) as an initiator and a Lewis acid (MX_n) as an activator/catalyst (Scheme 1). The latter reversibly activates (heterolytically dissociates) the covalent C-A bond in the initiator to generate "active" carbocation, and the reversible activation is responsible for decreasing the instantaneous concentration of the carbocationic growing species. A wide variety of the initiator/catalyst combination have been developed, but most of the initiators are confined to strongly acidic compounds such as hydrogen halides[2] and carboxylic acids[3] or cationogens such as *tert*-alkyl halides, esters, and ethers.[4]



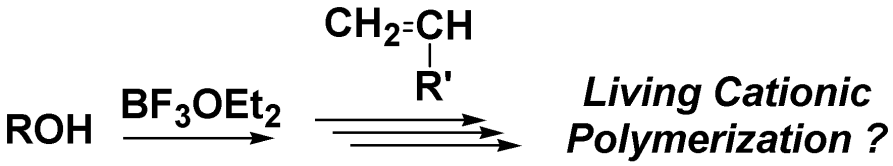
Scheme 1. Living Cationic Polymerization with Binary Initiating System

In conventional and living cationic polymerization as well as related organic reactions (e.g., electrophilic addition and Friedel-Crafts reactions), alcohols are strong nucleophiles and thereby powerful terminating and chain-transfer agents that convert cationic intermediates into the corresponding alkoxides, ω-olefins, etc. On the other hand, as a poison may sometimes be a good medicine, selected alcohols may work as protogens or initiators, when applied in a controlled and small concentration similar to water. Similarly important are water adducts (H-CH_2-CHR-OH) of a vinyl monomer[5] and tertiary or cumyl alcohols,[6] which have been employed as initiators for living/controlled cationic polymerization, where OH^-

counteranions are accompanied by the cationic species. These backgrounds indicate the possibility that even simple alcohols can work as initiators for living cationic polymerization; however, to the author's knowledge, no example of such system have been reported. If alcohols can be used as initiators, the system would be easily accessible for any chemists to construct well-defined polymers, and also the wide variation and presence in many kinds of molecules might contribute to stereospecific control via molecular design or conjugation with various molecules. However, alcohols should be more poisonous for carbocation than water, from the standpoint of miscibility for organic system, and most seriously, methanol effectively caps the carbocation to give methoxy in living cationic polymerization of vinyl ether, and also most Lewis acid catalysts are deactivated by alcohol. From these understandings, development of alcohol-initiated controlled system should be a challenging subject.

Sawamoto and co-workers have recently found out that borontrifluoride etherate (BF_3OEt_2) was available as an activator for controlled cationic polymerization even in the presence of water and alcohols, coupled with suitable initiators.[5] The borontrifluoride is likely tolerant to such polar groups and able to keep the Lewis acidity to catalyze controlled cationic polymerization under such hydrophilic condition, distinguished from the chloride (BCl_3) and other halogenated Lewis acids, such as $SnCl_4$, $TiCl_4$, and $EtAlCl_2$.

Thus, the author embarked on alcohol-initiated living cationic polymerization with BF_3OEt_2 as a catalyst, focusing on utilization of simple alkyl alcohols (ROH) as a proton source or cationogen (Scheme 2). For polymerization of isobutyl vinyl ether (IBVE), any alkyl alcohols showed a fair function as initiators regardless of the alkyl group (R–) to give well-controlled molecular weight and its distribution, although they needed aid of dimethyl sulfide as an additive for the control. The living-character was demonstrated by successful monomer-addition experiment and analyses of terminal structure of the produced polymer. Also, the system was applicable for variety of alkyl vinyl ethers and *p*-methoxystyrene.



Scheme 2. Alcohol/BF_3OEt_2 Binary System for Living Cationic Polymerization

Results and Discussion

1. Living Polymerization with MeOH.

Effects of Added Base First, the author employed most simple alcohol, methanol (MeOH), as an initiator for BF_3OEt_2-catalyzed cationic polymerization of isobutyl vinyl ether (IBVE) in CH_2Cl_2 at -15 °C (Figure 1; $[IBVE]_0$ = 1.0 M, $[MeOH]_0$ = 10 mM, $[BF_3OEt_2]_0$ = 24 mM). Even in the presence of MeOH, IBVE was rapidly polymerized, however the molecular weight distributions (MWDs) of the produced poly(IBVE)s were pretty broad, indicating that the system was lack of control. The number-average molecular weight (M_n) of products became much lower than those with MeOH-free system, which certainly demonstrated possibility of initiator-function of MeOH.[7] The author then examined an addition of Lewis bases to control the system, which are known to be effective for the control through interaction with growing carbocations for the stabilization or with activators for making the Lewis acidity milder.[8] Amount of the added base was followed by the previous papers. The polymerization rate was mostly decreased by the addition, indicating some interaction of the base with growing carbocation or BF_3OEt_2, however the MWDs of produced poly(IBVE)s were still uncontrolled (M_w/M_n > 2) for oxygen-based bases, e.g., ethyl acetate (AcOEt), 1,4-dioxane (DO), tetrahydrofuran (THF), and diethyl ether (Et_2O). In contrast, MWD became much narrower (M_w/M_n < 1.25) specifically by an addition of dimethyl sulfide (Me_2S). As shown in Figure 2, the M_ns of obtained polymers increased in direct proportion to monomer conversion and were in good agreement with the calculated values assuming that

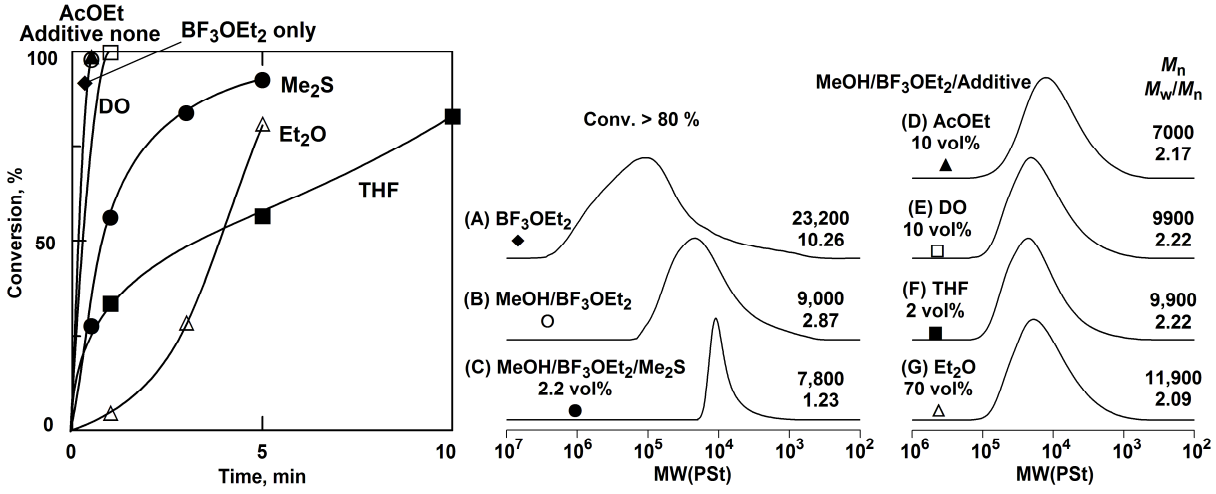


Figure 1. Time–conversion curves and SEC curves of poly(IBVE) obtained with $MeOH/BF_3OEt_2$ in the presence of additive: $[IBVE]_0$ = 1.0 M; $[MeOH]_0$ = 0, 10 mM; $[BF_3OEt_2]_0$ = 24 mM in CH_2Cl_2 at -15 °C.

one MeOH molecule generates one poly(IBVE), and MWDs were narrow throughout the polymerization. Webster et. al. presented that sulfide reduces the concentration of the propagating carbocation of poly(vinyl ether) via a reversible formation of stable sulfonium ion and this leads to controlled polymerization even using strong protonic acid, trifluoromethanesulfonic acid.[8c] In the author's system, there would be also similar contribution to stabilization of the cationic species leading to the control.

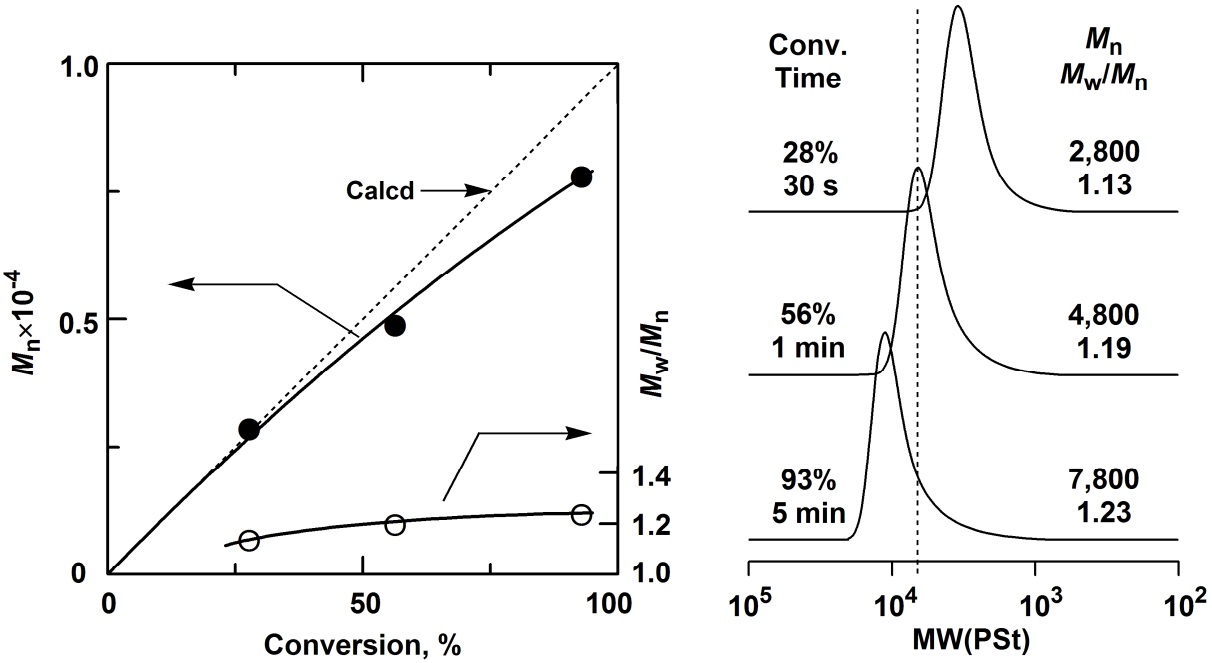


Figure 2. M_n, M_w/M_n and SEC curves of poly(IBVE) obtained with MeOH/BF_3OEt_2 in CH_2Cl_2 at -15 °C: $[IBVE]_0$ = 1.0 M; $[MeOH]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 300 mM.

Evidence for Initiator-Function of MeOH The author then carried out the polymerization with BF_3OEt_2 and Me_2S, coupled with various feed of MeOH ($[MeOH]_0$ = 10, 20, 50 mM) and compared the molecular weight of the product, to examine function of MeOH as an initiator (Figure 3). As the amount of MeOH was increased, the molecular weight was decreased and the value agreed with the calculated one, assuming that one polymer chain is generated from one molecule of MeOH. This result indicates an initiator-function of MeOH in the system. The MWD became a little broader in proportion as the amount of MeOH, and possibly an injection of too much amount of MeOH induced some side reactions, mainly as chain transfer reactions.

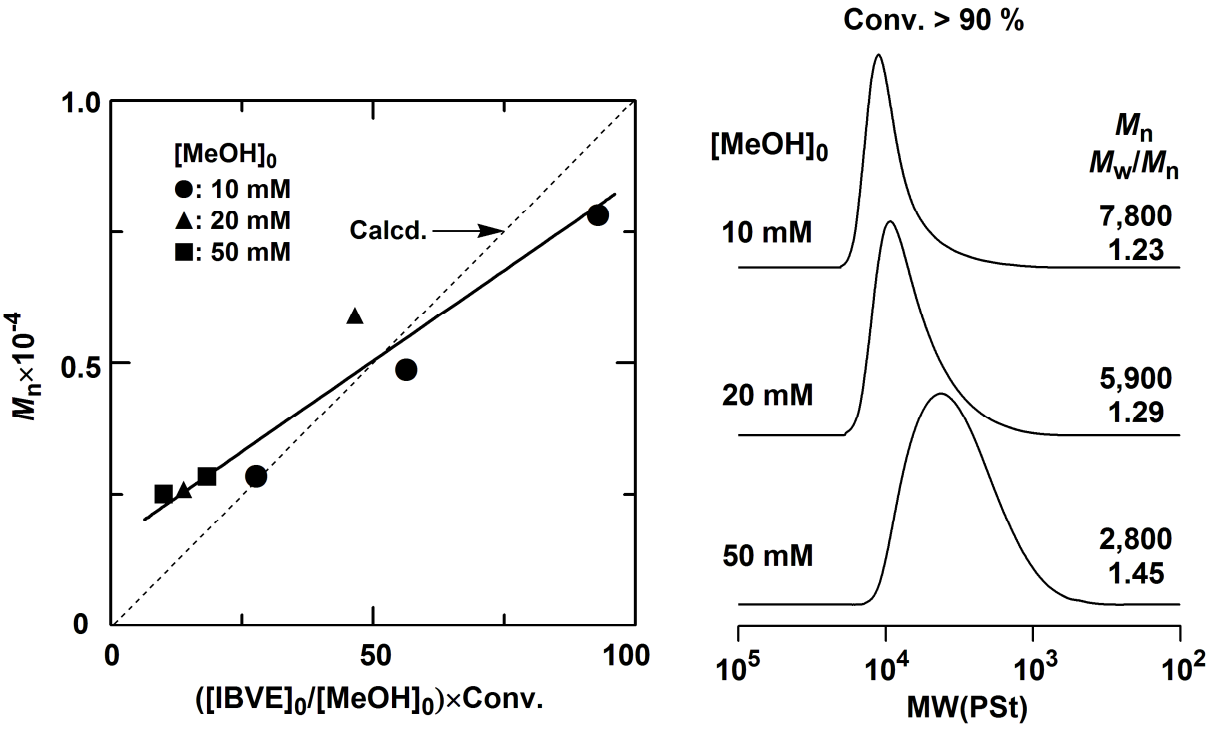


Figure 3. Control of molecular weight of poly(IBVE): $[IBVE]_0$ = 1.0 M; $[MeOH]_0$ = 10, 20, 50 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 300 mM in CH_2Cl_2 at -15 °C.

Living Character of the MeOH-initiating System To investigate whether the MeOH-initiating system is really living polymerization, a fresh feed of monomer was added to the reaction mixture when the initial charge of monomer was almost consumed (conversion = 93 %). After addition, the polymerization proceeded at nearly the same rate as in the initial stage (Figure 4). The M_n further increased with monomer conversion, and the peak of the MWD curves shifted to higher molecular weight region keeping the narrow distributions. From this result, this system is really "living polymerization", even though MeOH is employed.

Furthermore, the structure of obtained poly(IBVE) was analyzed with ^{1}H NMR. Figure 5 shows the ^{1}H NMR spectrum of poly(IBVE) with MeOH/BF_3OEt_2/Me_2S after quenching with excess amount of MeOH. In addition to the large peak due to the IBVE repeat units (*b*, *c*, *f*, *g*, *h*), two small signals assignable to the end group appeared: one derived from methyl group at α-end (a; 1.1 ppm), and another from methine of the terminal acetal at ω-end (*d*; 4.6 ppm). Peaks from terminal olefin, generated via β-proton elimination, were not observed. The functionality of ω-end, calculated from the ratio of M_n(GPC)/M_n(NMR, ω), was close to 1 [F_n(ω) = 1.11]. This result suggests that produced poly(IBVE) is fairly uniform because of no side-reactions.

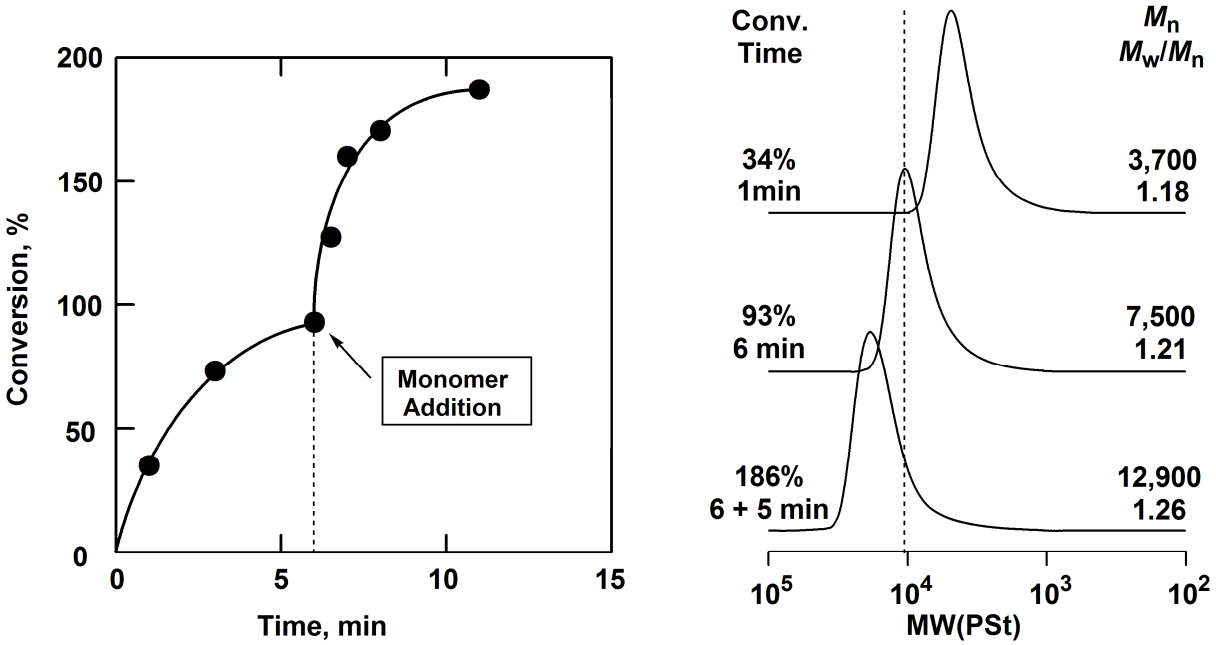


Figure 4. Monomer addition experiment in polymerization of IBVE with MeOH/BF_3OEt_2 in CH_2Cl_2 at -15 °C: $[IBVE]_0$ = $[IBVE]_{add}$ = 1.0 M; $[MeOH]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 300 mM.

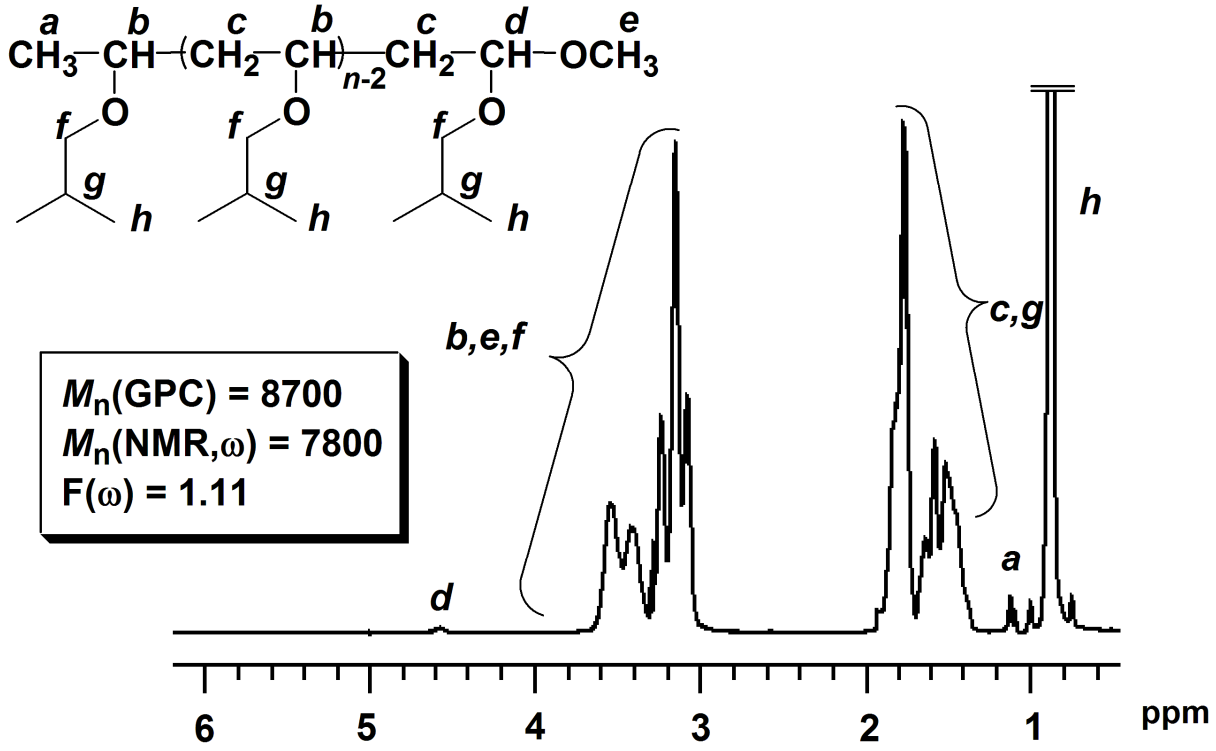


Figure 5. ^1H NMR spectrum of poly(IBVE) obtained with MeOH/BF_3OEt_2/Me_2S in CH_2Cl_2 at -15 °C: $[IBVE]_0$ = 1.0 M; $[MeOH]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 300 mM.

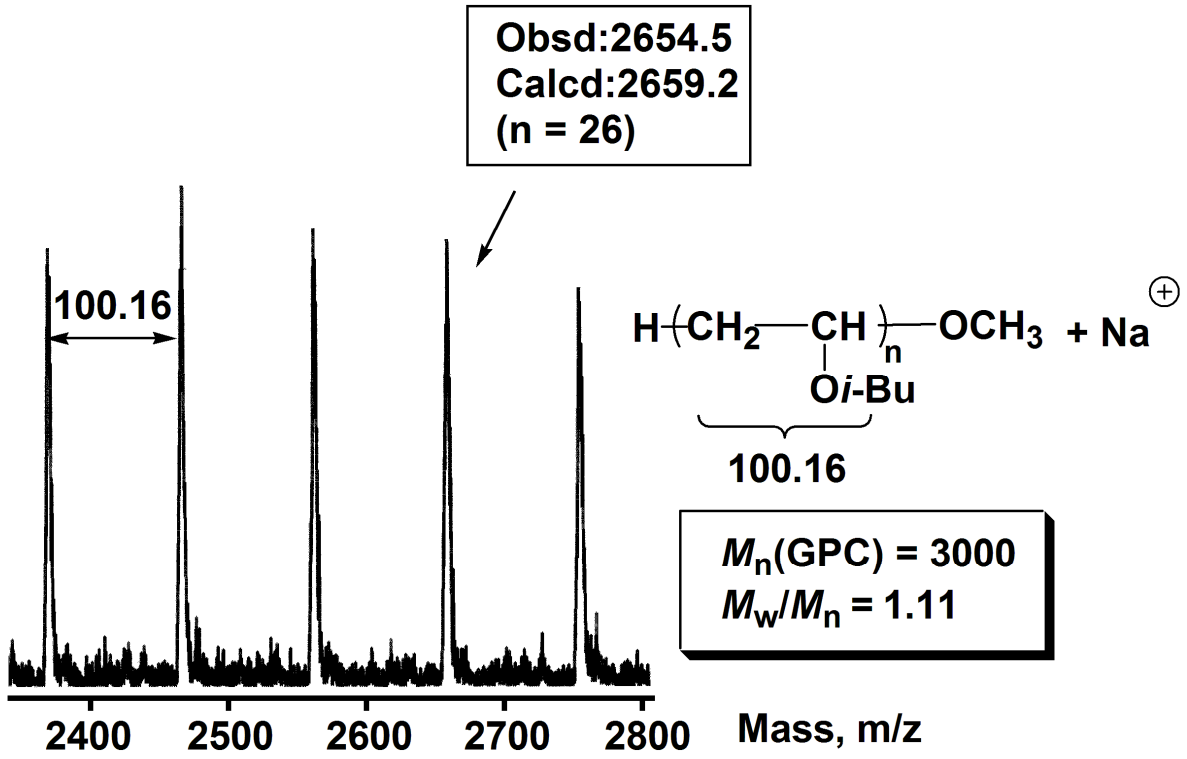


Figure 6. MALDI-TOF-MS spectrum of poly(IBVE) obtained with MeOH/BF_3OEt_2/Me_2S in CH_2Cl_2 at -15 °C: $[IBVE]_0$ = 1.0 M; $[MeOH]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 300 mM.

The uniformity of poly(IBVE) was also supported by MALDI-TOF-MS (Figure 6). The spectrum consists of a single series, all separated by 100.16 mass unit, corresponding to the molecular weight of IBVE monomer. The mass value of each peak agreed with that calculated from the predicted structure [H–(IBVE)$_n$–OCH_3] along with mass of Na^+.

Thus, these results demonstrated that this system is well-controlled without significant side reactions such as β-proton elimination even though an initiation from proton of MeOH.

2. Living Polymerization with Various Alcohols and Water.

Other alcohols and water (Chart 1) were also employed as initiators for the polymerization of IBVE with BF_3OEt_2/Me_2S in CH_2Cl_2 at -15 °C (Table 1). Independently of these species, the polymerizations occurred smoothly and were completed at similar rate (~5 min), which would be due to little difference in the acidity among them.[9] The M_ns of the obtained polymers were in good agreement with calculated values assuming that one polymer chain is generated from one alcohol, and the MWDs were narrow (M_w/M_w < 1.23). These results show that any hydroxy compounds, alcohols and water, are available as protongens or initiators for the BF_3OEt_2/Me_2S catalyzed system.

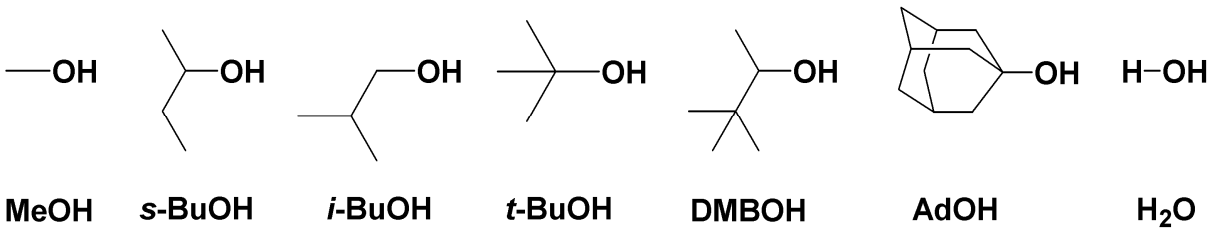


Chart 1. Structures of Hydroxy Compounds in This Work

The author expected that the alcohol-initiating system would be promising for control of stereospecificity because of the following points: 1) the alcohols are weaker acids than the conventional protonic acid initiators, such as halogen acids or acetic acid derivatives, and hence the generated counteranion (OR^-) would be "tighter" or closer to carbocation; 2) the diversity of alcohol facilitate environmental design of the counteranion in terms of bulkiness, symmetry or chirality. Thus, meso dyads (isotacticity) of poly(IBVE)s with various alcohols were determined from the signals of main-chain methylene carbon in ^{13}C NMR spectra [C_6D_6/CCl_4 (9/1 v/v) at 55 °C].[10] However, the meso contents were similar to the conventional values under same condition (solvent/temperature) and less dependent on the alcohol structure. From this result, the author then studied the polymerization at lower temperature in a less polar solvent with more elaborate alcohols regarding bulkiness or chirality toward stereospecific system, which will be reported in Chapter 2.

Table 1. Various Alcohols as Initiators for Living Cationic Polymerization[a]

Entry	Initiator	Conv, %	M_n	M_w/M_n	meso, %
1	MeOH	93	7,800	1.23	59
2	*s*-BuOH	90	9,600	1.10	60
3	*i*-BuOH	89	8,600	1.19	58
4	*t*-BuOH	90	8,100	1.17	60
5	DMBOH	92	8,900	1.13	59
6	AdOH	87	8,500	1.18	60
7	H_2O	86	8,200	1.21	58

[a] Conditions: $[IBVE]_0$ = 1.0 M; $[alcohol]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 300 mM in CH_2Cl_2 at -15 °C, polymerization time: 5 min.

3. Living Polymerization of Various Monomers with MeOH.

Finally, the MeOH initiating system was applied for various alkyl vinyl ethers [alkyl: ethyl (EVE); cyclohexyl (CHVE); *t*-butyl (TBVE); chloroethyl (CEVE)] and *p*-methoxystyrene (pMOS) (Chart 2). In cationic polymerization, the reactivity of monomer is more enhanced as the substituent is more electron-donating. According to the monomer reactivity, the amount of Me_2S and temperature were adjusted as follows: larger amounts of additive and lower temperature were employed for more reactive monomer such as CHVE and TBVE than IBVE, while smaller amounts of additive and higher temperature for less reactive monomer such as CEVE and pMOS. For all monomers, the polymerization proceeded smoothly and quantitatively and the M_ns of the polymers were close to calculated values assuming that one polymer chain form per MeOH molecule and the MWDs were narrow (Table 2). Thus, as far as the amount of Me_2S and temperature are adjusted, the MeOH/BF_3OEt_2 initiating system was applicable for versatile monomers to produce well-defined polymers.

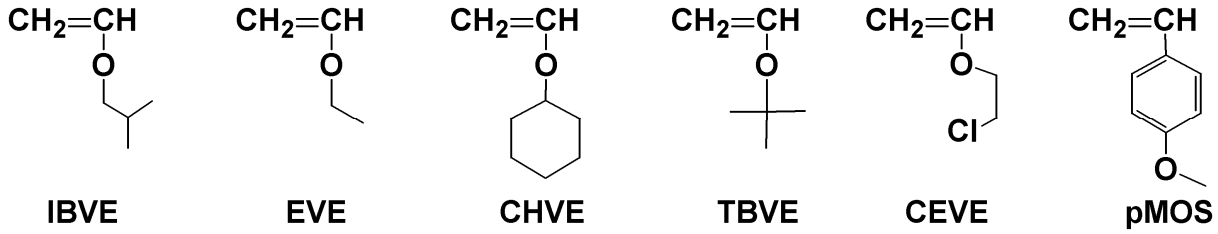


Chart 2. Structures of Monomers in This Work

Table 2. Living Cationic Polymerization of Various Monomers with Alcohol/BF_3OEt_2 Initiating Systems[a]

Entry	Monomer	Temperature, °C	Me_2S, mM	Time	Conv, %	M_n	M_w/M_n
1	IBVE	-15	300	5 min	93	7,800	1.23
2	EVE	-15	300	5 min	89	8,200	1.20
3	CHVE	-40	1,000	40 min	85	7,700	1.18
4	TBVE	-78	300	8 h	84	6,200	1.25
5	CEVE	-15	100	6 h	91	7,000	1.19
6	pMOS	20	30	3 h	93	9,400	1.06

[a] Conditions: $[Monomer]_0$ = 1.0 M; $[MeOH]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 30-1000 mM in CH_2Cl_2.

Conclusion

While conventionally terminators or chain-transfer agents, alcohols turned out to be surprisingly effective initiators for living cationic polymerization of VEs and pMOS, coupled with BF_3OEt_2 as a catalyst and Me_2S as a basic additive, potentially opening a way to design the structure and functions of the counteranion via a wide variety of ubiquitously available alcohols. The polymerization with various alcohols gave polymers with molecular weights that increased in direct proportion to monomer conversion and agreed well with the calculated values, assuming that one initiator molecule generated one polymer chain, with narrow distributions ($M_w/M_n \sim 1.2$).

Experimental Section

Materials

IBVE (Tokyo Kasei; purity > 99%), ethyl vinyl ether (EVE, Tokyo Kasei; >99%), cyclohexyl vinyl ether (CHVE, Nippon Carbide Industries), *tert*-butyl vinyl ether (TBVE, Aldrich; 98%), chloroethyl vinyl ether (CEVE, Tokyo Kasei; >97%) were washed with 10% aqueous sodium hydroxide and then with water, dried overnight over potassium hydroxide, and distilled twice from calcium hydride before use. *p*-Methoxystyrene (pMOS, Aldrich; 97%) was washed with 10% aqueous sodium hydroxide and then with saturated aqueous sodium chloride, dried overnight over sodium sulfate, distilled from calcium hydride under reduced pressure, and stored at -80 °C. Methaol (MeOH, Wako; 99.5%) was distilled over magnesium, *tert*-butanol (*t*-BuOH, Wako; >99%) was distilled over calcium hydride, and 2-butanol (*s*-BuOH, Aldrich; >99.5%), isobutyl alcohol (*i*-BuOH, Wako; >99%) and 3,3-dimethyl-2-butanol (DMBOH, Aldrich; 98%) were dried over molecular sieves 4A 1/16 before use. Distilled deionized water was used as a form of saturated solution in CH_2Cl_2 ($[H_2O]$ = 125 mM at 25 °C).[11] Carbon tetrachloride (an internal standard for gas chromatography) and ethyl acetate (AcOEt) were dried overnight over calcium chloride and distilled twice from calcium hydride. 1,4-Dioxane (DO), tetrahydrofuran (THF), and diethyl ether (Et_2O) were dried overnight over calcium chloride and distilled from sodium benzophenone ketyl. Dimethyl sulfide (Me_2S) was dried overnight over calcium chloride and distilled from sodium. 1-Adamantanol (AdOH, Aldrich; 99%) and BF_3OEt_2 (Aldrich) were

used as received. CH_2Cl_2 (solvent) was passed through purification column (Solvent Dispensing System; Glass Contour) before use.

Polymerization Procedure

Polymerization was carried out under dry nitrogen in baked glass tubes equipped with a three-way stopcock. A typical example for IBVE polymerization with MeOH is given below: The reaction was initiated by adding solutions of BF_3OEt_2 (0.3 mL) in CH_2Cl_2 via a dry syringe into a mixture (2.7 mL) of IBVE (0.39 mL) and CCl_4 (0.20 mL) containing MeOH in CH_2Cl_2 at -15 °C. After a predetermined interval, the polymerization was terminated with prechilled methanol containing a small amount of ammonia. Monomer conversion was determined from its residual concentration measured by gas chromatography with CCl_4 as an internal standard. The quenched reaction mixture was washed with dilute hydrochloric acid, aqueous sodium hydroxide solution and water to remove initiator residues, evaporated to dryness under reduced pressure, and vacuum-dried to give the polymer.

Measurements

The M_n, M_w/M_n, and MWD curves of the polymers were determined by size-exclusion chromatography in chloroform at 40 °C using three polystyrene gel columns [Shodex K-805L (pore size: 20-1000 A; 8.0 mm i.d. × 30 cm) × 3; flow rate 1.0 mL/min] that were connected to a Jasco PU-980 precision pump, a Jasco RI-930 refractive index detector. The columns were calibrated against 13 standard poly(styrene) samples (TOSOH; M_n = 500-3,840,000; M_w/M_n = 1.01-1.14). ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA500 spectrometer in $CDCl_3$ at room temperature operating at 500.2 MHz (^1H) or in CCl_4/C_6D_6 (9/1) at 55 °C operating at 125.83 MHz (^{13}C), respectively. MALDI-TOF-MS analysis was performed on a Perspective Biosystems Voyager-DE STR spectrometer, equipped with a 2 m linear flight tube and a 337 nm nitrogen laser, with dithranol (1,8,9-anthracenetriol) as an ionizing matrix and sodium trifluoroacetate as a cationizing agent. Polymer samples for NMR and MALDI-TOF-MS were fractionated by preparative SEC (column: Shodex K-5002F).

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Chapter 2

Molecular Design of Counteranion with Alcohol: Dual Control of Molecular Weight and Tacticity in Cationic Polymerization

Abstract

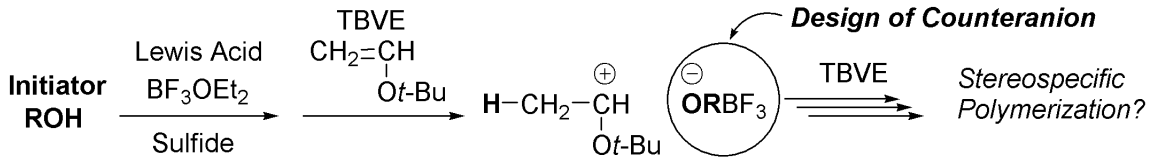
Toward dual control over molecular weight and tacticity, molecular design was conducted for molecules around growing carbocation in alcohol-initiated cationic polymerization of *tert*-butyl vinyl ether (TBVE) with BF_3OEt_2 (catalyst) and a sulfide (additive). When the polymerizations were done in toluene at -78˚C, various commercially available alcohols and phenols gave long-lived polymers with narrow molecular weight distributions. The tacticity of the produced polymers was somewhat dependent on the structure of the initiator: higher isotacticity was obtained with alcohols carrying bulkier substituents and less acidic phenols. The molecular design was also directed to the sulfide additive. Sulfide-alcohols were newly designed as "initiator built-in additives" to make the interaction between carbocation and counteranion tighter via sulfide for more advanced tacticity control. The isotacticities became a little higher than the alcohol-initiating systems in conjunction with the sulfide, without serious loss of the molecular weight controllability.

Introduction

Various initiating systems for living cationic polymerization have been developed along with a variety of combination of a protonic acid (HA) and a Lewis acid (MX_n), where the latter as a catalyst activates the terminal covalent bonds (~~~C-A) from the former to give carbocations (~~~C^+) and counteranion (A^-MX_n).[1] Some systems are now useful tools to produce "well-defined" polymers of predetermined molecular weight and uniform terminal structures with electron rich vinyl monomers (e.g., vinyl ethers, styrenes, isobutylene, etc.). However, control over the direction of the substituent is still difficult in cationic polymerizations, and thus the obtained polymers are "ill-defined" in terms of tacticity. As demonstrated by some stereospecific polymers via metal-coordination[2] and anionic[3] polymerization, tacticity is an important structural factor for advanced physical properties.

There are some literatures to study tacticity control on cationic polymerizations. Ohgi and Sato studied effects of the ligand for BF_3 complex (catalyst) on stereoregularity in the conventional cationic polymerization of *tert*-butyl vinyl ether (TBVE) toward stereoregular poly(vinyl alcohol)s.[4] They thus found that the isotacticity was influenced by the size of BF_3 complex forming the counteranion during the polymerization, and eventually 79% of triad isotacticity (*mm*) was achieved with BF_3OEt_2 catalyst. Sawamoto and Ouchi et. al. have also examined structural effects of the catalyst on stereoregularity for polymerization of isobutyl vinyl ether (IBVE) with a series of bisphenoxy titanium(IV) dichloride [$TiCl_2(OAr)_2$], based on the "living" cationic polymerization system in conjunction with the HCl adduct of IBVE as an initiator.[5] Consequently, highly isotactic poly(IBVE) (m = 92%) was obtained with bis[(2,6-diisopropyl)phenoxy]titanium dichloride, however the polymerization was lack of control for molecular weights. Thus, a dual control over chain length (molecular weight) and side chain direction (tacticity) is a challenging issue in cationic polymerizations as well as the higher tacticity control.[6]

Under these backgrounds, the author has recently found that alcohol works as an effective initiator or a proton source for living cationic polymerization, coupled with BF_3OEt_2 (catalyst) and Me_2S (additive).[7] In this system, the alcohol (ROH) gave proton (H^+) along with counteranion consisting of alkoxy anion (RO^-) and BF_3, and various kinds of alcohols were available for the control as the initiators. Here, the generated counteranion, RO^-, is likely tighter to the growing carbocation because of its high nucleophilicity, and thus the structural design of the counteranion is expected to be sensitive for the direction of incoming



Scheme 1. Design of Counteranion with Alcohols toward Stereospecific Polymerization

monomers. This feature of the alcohol initiating system encouraged him to develop dual control of molecular weight and tacticity through modification of this system (Scheme 1). The author chose TBVE as the monomer, because the resultant poly(TBVE) can be converted into poly(vinyl alcohol) by acidic treatment, whose tacticity control is desired for advanced physical properties based on the more effective intra- and intermolecular hydrogen bonding.[8]

Results and Discussion

1. Polymerization Condition (Temperature and Solvent).

The author first examined effects of the polymerization condition (i.e., temperature and solvent) on molecular weight control using MeOH as an initiator, in conjunction with BF_3OEt_2 (catalyst) and Me_2S (additive) (Figure 1).

When the polymerization was done in toluene at 0 or -40 ˚C, the monomer was instantly consumed (within 30 sec) to give uncontrolled polymers with broad molecular weight distributions (MWDs) [Figure 1(A) and (B): $M_w/M_n \sim 3$]. The higher reactivity of TBVE would cause the uncontrolled fashion under these conditions. However, when the temperature was decreased to -78˚C, the polymerization rate got much smaller (4 hours for 93% conversion) and the molecular weight distributions became narrower [Figure 1(C): M_w/M_n = 1.1–1.2]. Although the molecular weights were higher than the theoretical values

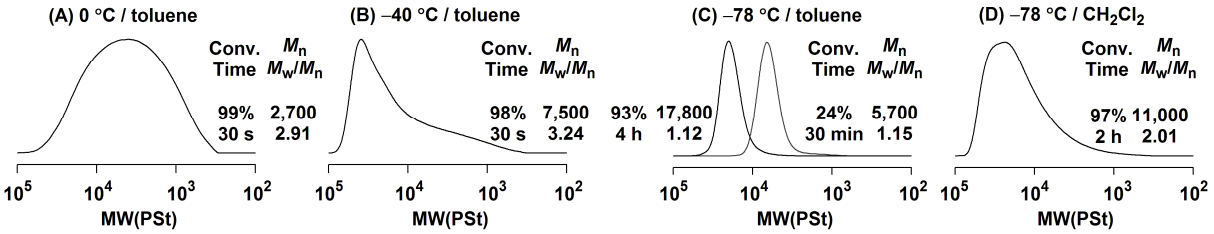


Figure 1. Effects of polymerization conditions on the cationic polymerization of TBVE with MeOH/BF_3OEt_2/Me_2S: $[TBVE]_0$ = 1.0 M; $[MeOH]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 10 mM in toluene, CH_2Cl_2 at 0, -40, -78 °C.

(calculated from the injection ratio of TBVE to the alcohol and the conversion), the SEC curves shifted as the conversion keeping the unimodal shapes, which indicates an existence of "living" species. On the other hand, the polymerization got less controlled in CH_2Cl_2 [Figure 1(D): M_w/M_n > 2.0]. The author thus decided to modify the initiator fixing the condition "in toluene at –78˚C" toward a dual control over molecular weight and tacticity. Note that the condition of "in less polar solvent at lower temperature" is favorable for tacticity control in the cationic polymerization, as shown by some literatures.[4,5]

2. Design of Counteranion with Alcohols.

Thus, various alcohols including water were employed as initiators for the cationic polymerization of TBVE with BF_3OEt_2/Me_2S in toluene at -78 °C (Chart 1). Here, they were all commercially available, and chosen in terms of bulkiness, asymmetry, and chirality, etc. As shown in Table 1, all the alcohol reagents induced polymerizations to give higher conversions in moderate time, and affected not only polymerization rates but also molecular weights and their distributions of the obtained polymers. Some of them gave highly uniform polymers with narrow MWDs less than 1.15: MeOH (entry 1), (*rac*)-*s*-BuOH (entry 2), (*R*)-*s*-BuOH (entry 3), DMBOH (entry 5), (–)-Menthol (entry 9), and BzOH (entry 11). However, most of the polymers exhibited higher molecular weights than the theoretical values, which would be caused by the low initiation efficiency of the alcohol.

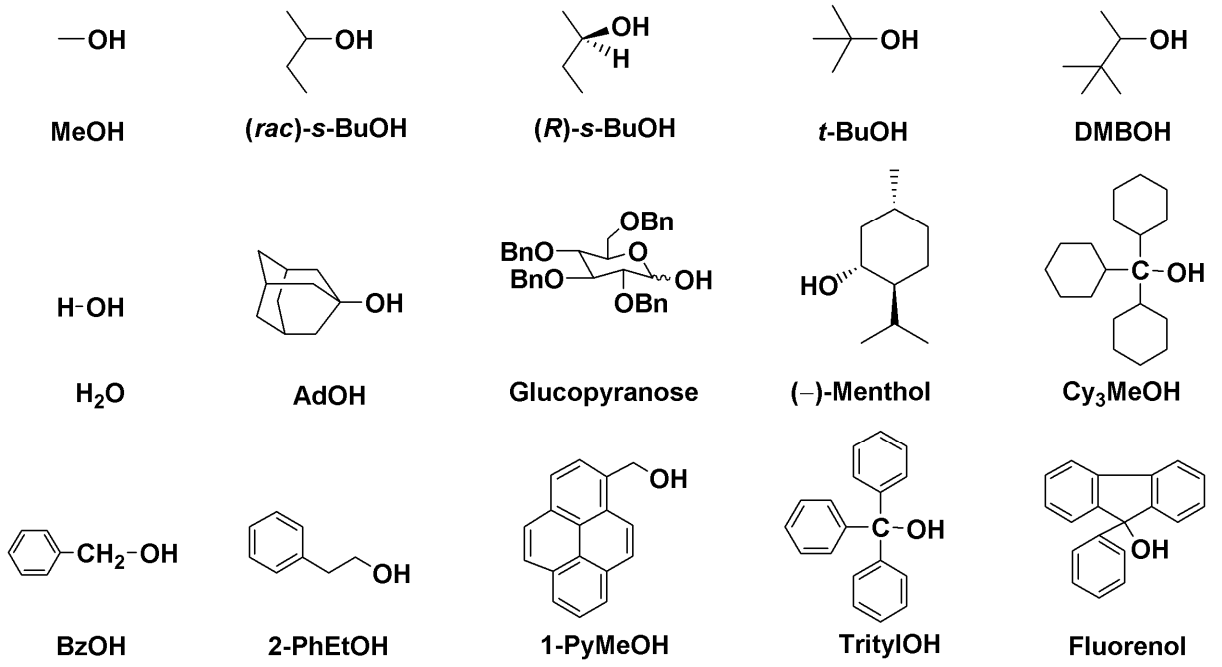


Chart 1. Structures of Alcohols Employed in This Work

Table 1. Effects of Initiators on the Tacticity[a]

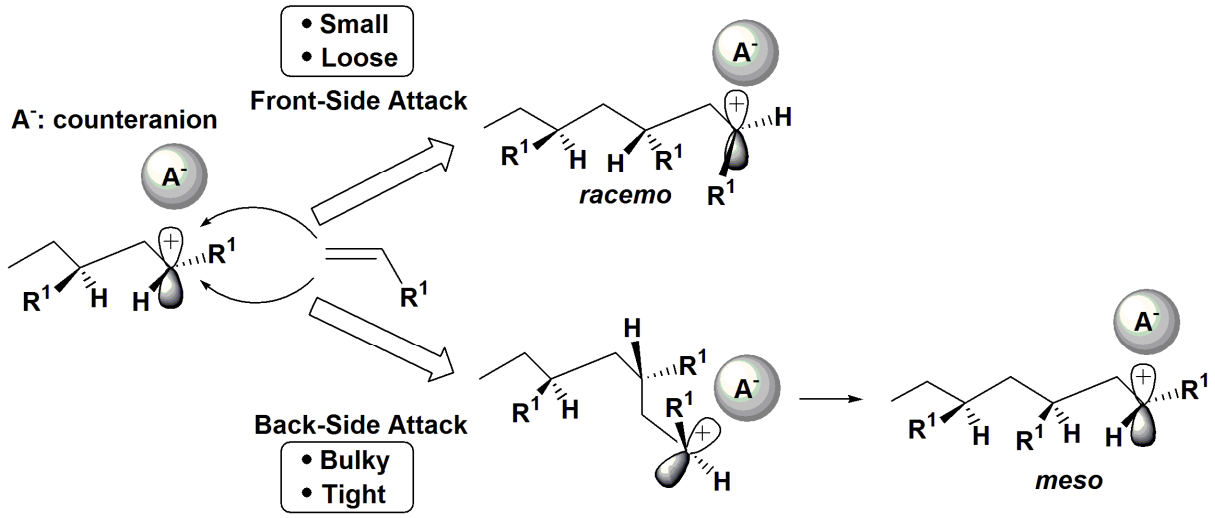
Entry	Initiator	Time, h	Conv, %	M_n	M_w/M_n	*mm*, %	*mr*, %	*rr*, %
1	MeOH	4	93	17,800	1.12	58.3	36.2	5.5
2	(*rac*)-*s*-BuOH	3	93	14,500	1.11	62.0	33.4	4.6
3	(*R*)-*s*-BuOH	3	98	12,900	1.14	61.4	33.9	4.7
4	*t*-BuOH	1	93	10,100	1.15	58.8	34.8	6.4
5	DMBOH	5	90	16,100	1.13	62.4	33.6	4.0
6	H_2O	0.83	98	9,100	1.34	60.1	33.9	6.1
7	AdOH	1	84	9,800	1.20	61.4	33.4	4.6
8	Glucopyranose	6	93	15,300	1.28	62.4	33.4	4.2
9	(−)-Menthol	1.5	94	12,200	1.10	60.7	34.2	5.1
10	Cy_3MeOH	5	71	14,800	1.28	61.0	33.6	5.3
11	BzOH	2	90	13,900	1.13	58.2	36.7	5.1
12	2-PhEtOH	8	89	18,600	1.22	59.3	35.3	5.7
13	1-PyMeOH	5	88	14,600	1.32	61.5	33.5	4.6
14	TritylOH	8	96	17,600	1.21	62.1	33.8	4.1
15	Fluorenol	6	93	22,900	1.26	63.9	32.3	3.8

[a] Conditions: $[TBVE]_0$ = 1.0 M; $[initiator]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 10 mM in toluene at -78 °C.

The tacticities of the obtained poly(TBVE)s were determined by the peak intensity ratio from the main-chain methine carbon [-CH_2-***C***H(O*t*-Bu)-] around 65-69 ppm in ^{13}C NMR: this peak is known to be split into the three region based on the triad isotacticity (*mm*), heterotacticity (*mr*) and syndiotacticity (*rr*).[9] As shown in Table 1, the tacticity showed some dependence on the alcohol reagent: the isotacticity (*mm*) was changed on the range from 58.2% (BzOH: Entry 11) to 63.9% (Fluorenol: Entry 15). The bulkiness of the alcohol seemed to affect the tacticity: bulky alcohols such as TrytilOH and Fluorenol tended to give higher *mm* values (62.1% and 63.9% respectively) than the smaller alcohols [e.g., MeOH (58.3%) and BzOH (58.2%)]. On the other hand, the chirality had no effect on the tacticity (Entry 2 vs 3).

This trend might be reasonably interpreted with the mechanism, proposed by Kunitake

et. al. (Scheme 2). They mentioned that the important factors in controlling stereochemistry in cationic polymerizations are the physical size of counteranion and the tightness of the ion pair between the growing carbocation and its counteranion.[10] If the counteranion (A^-) is small and/or the interaction with the growing carbocation is weak, the incoming monomer attacks from the less hindered side, i.e. the same side of counteranion, leading to *racemo* unit to minimize the steric repulsion between the substituents in the monomer and the growing polymer (i.e., front-side attack). On the other hand, if the counteranion is bulky and/or the interaction with the growing carbocation is strong, the incoming monomer will attack from the opposite side of counteranion, leading to *meso* unit (i.e., back-side attack). The following is the discussion about the counteranion effects on tacticity control in the alcohol (ROH)-initiating systems, based on this mechanism (A^- = OR^-, R^1 = O*t*-Bu). In the polymerization with the bulkier alcohol (e.g., TrytilOH and Fluorenol), the bulkiness effect would dominate the conformation for the back-side attack, although the counteranion (OR^-) might be looser because of the steric hindrance with the pendent chain (O*t*-Bu), to give higher isotacticity than smaller alcohol. On the other hand, in the case with H_2O as an initiator, tighter ion pair due to the less hindrance would rather lead the back-side attack to increase the isotacticity.[4] Thus, it likely depends on the counteranion that either factor is predominant to determine the tacticity. Furthermore, as the compatibility of bulkiness and tightness is difficult, the isotacticity was not so increased. A construction of both tighter and bulkier environment around the growing cation would allow higher isotacticity even in the alcohol initiating system.



Scheme 2. Proposed Mechanism

3. Design of Counteranion with Phenols.

The author next employed a phenol derivative (ArOH: Chart 2) as the initiator instead of the alcohol, since the versatility on the benzene ring would be promising for the counteranion design in terms of electronic feature and bulkiness. Chart 2 shows phenols employed in this work as initiators for the cationic polymerization of TBVE with BF_3OEt_2/Me_2S. As shown with the pK_a values,[11] the acidity is obviously affected by the substituents and the position, and consequently the tightness of the counteranion could be modified along with the steric environment toward tacticity control.[12]

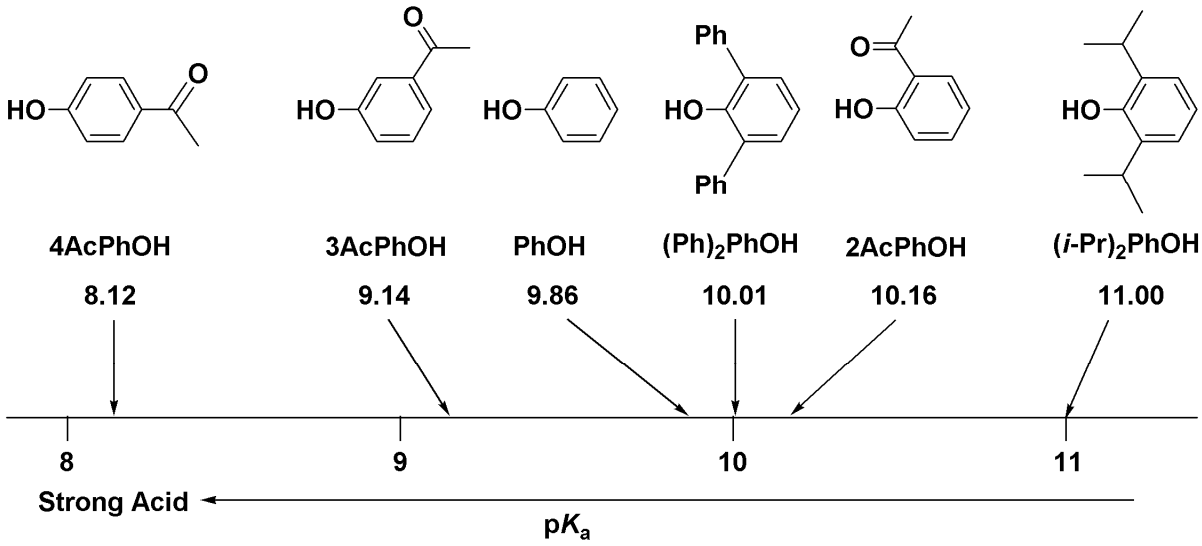


Chart 2. Structures of Phenols Employed in This Work

Even with these phenol initiators, the monomer consumptions were almost quantitative at moderate rates except for the non-substituted phenol. SEC curves of the obtained polymers shifted to higher molecular weight region as the conversion without changing the monodisperse shapes (Figure 2). Thus, phenol reagents found to be useful initiators for polymerization control in conjunction with BF_3OEt_2/Me_2S.

Tacticities of the obtained poly(TBVE)s were evaluated by ^{13}C NMR, and the *mm* values were plotted against pK_a of the phenol. As shown in Figure 3, they were increased as the pK_a value. Phenoxy anion from lower acidic phenol (larger pK_a) would be tighter for the growing cation to give isotactic propagation. However, the isotacticities were not so high, similar to those with alcohols.

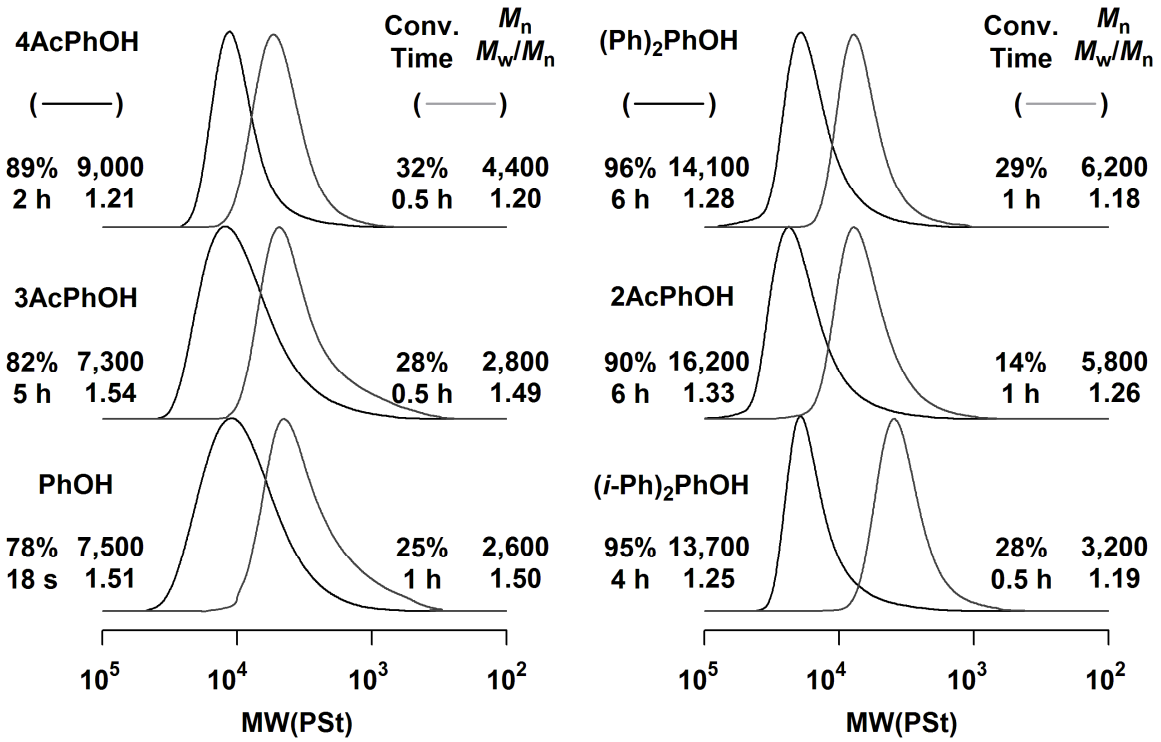


Figure 2. Phenol derivatives-initiated living cationic polymerization of TBVE with BF_3OEt_2/Me_2S: $[TBVE]_0$ = 1.0 M; $[phenol]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 10 mM in toluene at -78 °C.

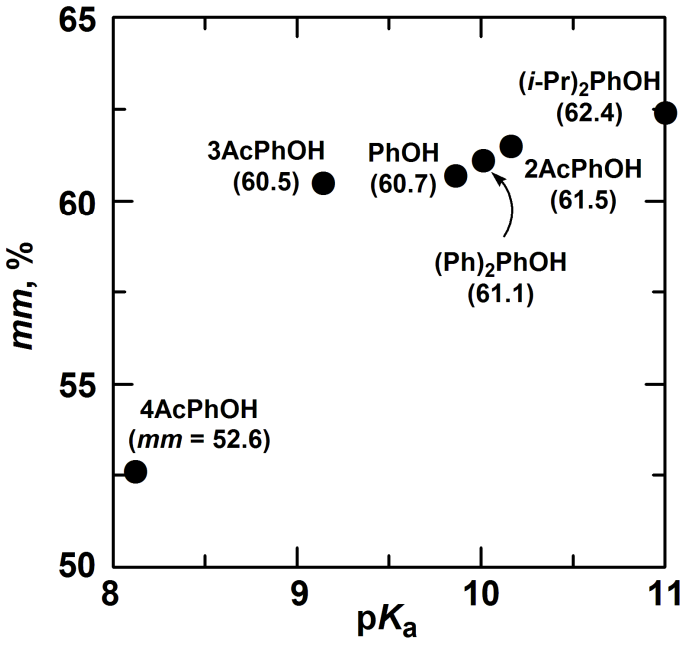
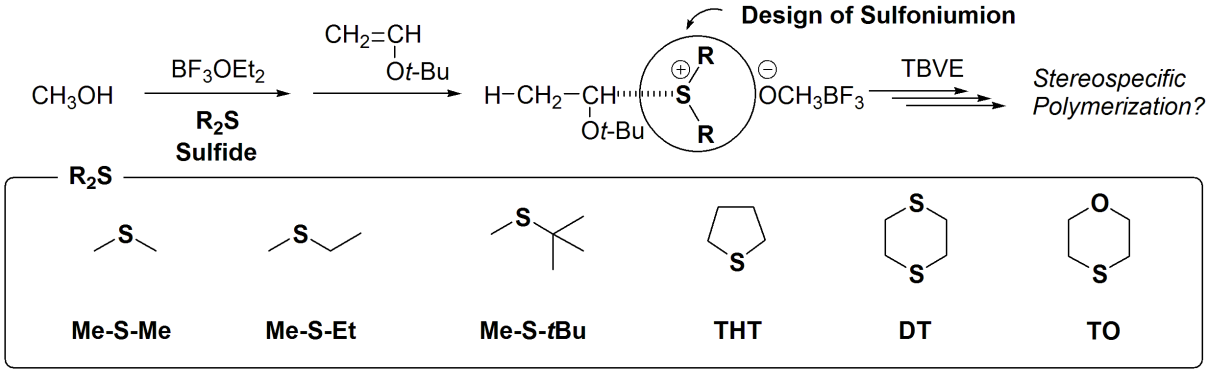


Figure 3. Effects of pK_a on the *mm* of poly(TBVE) obtained with phenols/BF_3OEt_2/Me_2S: $[TBVE]_0$ = 1.0 M; $[phenol]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[Me_2S]_0$ = 10 mM in toluene at -78 °C.

4. Effects of Sulfides.

As shown above, even though a variety of alcohols and phenols were employed as initiators, the isotacticity was not so increased (*mm* < 65%). The next effort was then directed to design of the sulfide additive, directly interacting with carbocation species for the stabilization via reversible formation of sulfonium ion (Scheme 3).[13] The author modified the sulfides from Me_2S to other sulfide reagents for the MeOH-initiated polymerization with BF_3OEt_2. However, as the bulkiness of the sulfide increased, the MWD became broader (M_w/M_n > 1.8: Table 2), which is due to that the essential formation of sulfonium ion is difficult because of the steric hindrance. However, the *mm* value was increased with the increase of the bulkiness. Thus, a formation of sulfonium ion was found to contribute to the molecular weight control, but to have a negative effect for the tacticity control.

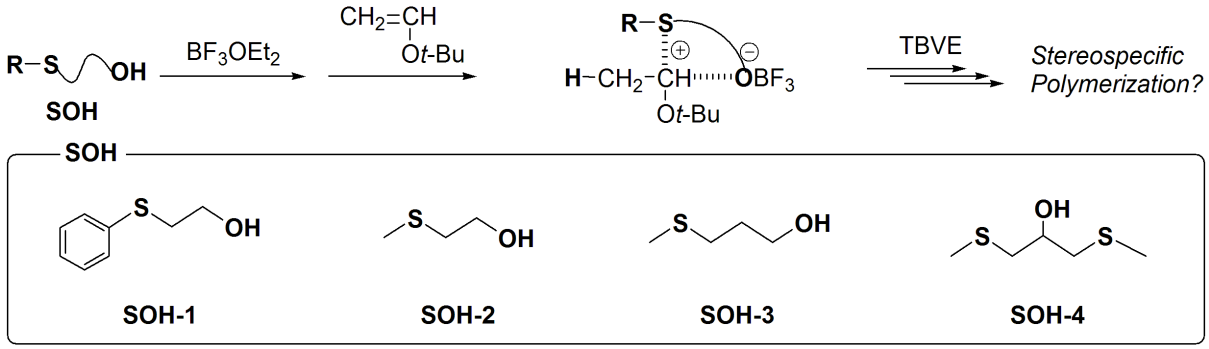


Scheme 3. Design of an Environment around the Growing Cation with Sulfide

Table 2. Effects of Sulfides on the Tacticity[a]

Entry	Sulfide	Time	Conv, %	M_n	M_w/M_n	*mm*, %	*mr*, %	*rr*, %
1	Me-S-Me	4 h	93	17,800	1.12	58.3	36.2	5.5
2	Me-S-Et	45 min	87	19,100	1.85	62.0	33.2	4.8
3	Me-S-*t*Bu	30 s	99	48,000	5.75	69.8	27.0	3.2
4	THT	30 min	97	14,500	2.21	63.4	32.2	4.4
5	DT	1 min	98	35,000	3.93	64.3	30.4	5.3
6	TO	30 s	98	36,800	5.00	67.8	28.4	3.8
7	none	1 min	92	29,200	12.69	70.4	26.2	3.4

[a] Conditions: $[TBVE]_0$ = 1.0 M; $[MeOH]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM; $[sulfide]_0$ = 10 mM in toluene at -78 °C.



Scheme 4. Design of an Environment around the Growing Cation with Sulfide-Alcohol

The difficulty in compatibility for dual control over molecular weight and tacticity is probably caused by looser interaction between the carbocation and the counteranion (OR^-) due to the formation of sulfonium ion in the molecular weight-controlled system. Based on this speculation, the author thus targeted sulfides covalently attached to alcohol moiety (sulfide-alcohol, SOH) as the "initiator built-in additive" to make the tighter interaction between carbocation and counteranion via sulfide. If the polymerization ideally proceeds with the sulfide-alcohol, both of sulfide and alkoxy anion in a single molecule interact with carbocation to construct tighter counteranion, which might lead to a dual control over molecular weight and tacticity (Scheme 4). Four kinds of sulfide-alcohol were then employed for cationic polymerization of TBVE with BF_3OEt_2: 2-(phenylthio)ethanol (SOH-1), 2-(methylthio)ethanol (SOH-2), 3-(methylthio)propanol (SOH-3), and 1,3-bis(methylthio)-2-

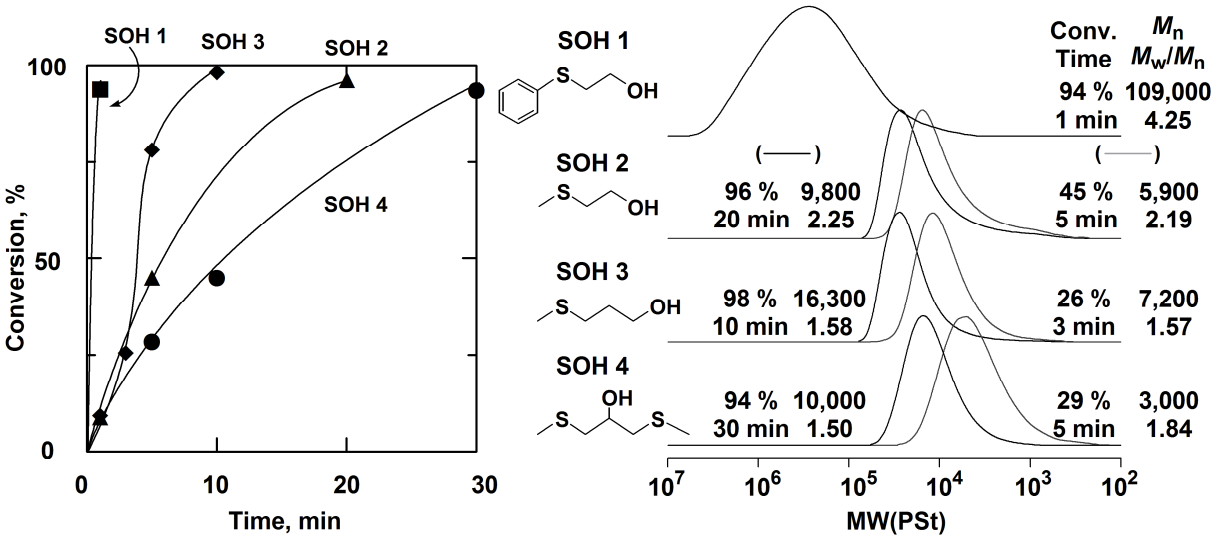


Figure 4. Time–conversion curves and SEC curves of poly(TBVE) obtained with SOH/BF_3OEt_2: $[TBVE]_0$ = 1.0 M; $[SOH]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM in toluene at -78 °C.

Table 3. Effects of Initiator Built-in Sulfides on the Tacticity[a]

Entry	Initiator	Time, min	Conv, %	M_n	M_w/M_n	*mm*, %	*mr,* %	*rr*, %
1	SOH-1	1	94	109,000	4.25	67.8	27.8	4.4
2	SOH-2	20	96	9,800	2.25	66.1	29.8	4.0
3	SOH-3	10	98	16,300	1.58	67.5	28.6	3.9
4	SOH-4	30	94	10,000	1.50	66.8	29.4	3.9

[a] Conditions: $[TBVE]_0$ = 1.0 M; $[initiator]_0$ = 10 mM; $[BF_3OEt_2]_0$ = 24 mM in toluene at -78 °C.

propanol (SOH-4). SOH-1 resulted in very fast and uncontrolled polymerization, while the three others induced fairly controlled polymerizations, although the MWDs were a little broad (Figure 4). The isotacticities were a little higher (*mm* = 66–68%) than the alcohol or phenol initiating systems, but unfortunately, much higher tacticity control was not achieved (Table 3). Further molecular design would be required to regulate the direction of incoming monomer.

Conclusion

Various alcohols and phenols were examined as initiators for cationic polymerization of TBVE with BF_3OEt_2 (catalyst) and a sulfide (additive) to achieve dual control of molecular weight and tacticity. The former control can be controlled under the suitable condition: at lower temperature (-78˚C) and in non-polar solvent (toluene). The latter was somewhat dependent on the structure of the initiator, and a bulkier alcohol gave higher isotacticity (e.g., Fluorenol: *mm* = 64%). In the case with phenols, the acidity (pK_a) affected the isotacticity rather than the steric factor: lower acidity gave higher isotacticity. The alcohols containing sulfide group were newly employed as "initiator built-in additive" to make tighter counteranion via sulfide. Some of them gave isotactic-rich poly(TBVE)s (*mm* = 68%), keeping the fair controllability for molecular weights.

Experimental Section

Materials

TBVE (Aldrich; purity = 98%) was washed with 10% aqueous sodium hydroxide and then with water, dried overnight over potassium hydroxide, and distilled twice from calcium hydride before use. Methanol (MeOH, Wako; 99.5%) was distilled over magnesium, *t*-butanol (*t*-BuOH, Wako; > 99%) and benzyl alcohol (BzOH, Aldrich; 99.8%) were distilled over calcium hydride, and 2-butanol (*s*-BuOH, Aldrich; >99.5%), 3,3-dimethyl-2-butanol (DMBOH, Aldrich; 98%), 2-phenylethanol (2-PhEtOH, Wako; 98%), 2'-hydroxyacetophenone (2AcPhOH, TCI; >98%), ethyl methyl sulfide (TCI; >96%), *tert*-butyl methyl sulfide (TCI; >98%), tetrahydrothiophene (THT, TCI; >99%), 2-(phenylthio)ethanol (SOH-1, TCI; >97%), 2-(methylthio)ethanol (SOH-2, TCI; >98%), 3-(methylthio)propanol (SOH-3, TCI; >99%), and 1,3-bis(methylthio)-2-propanol (SOH-4, Alfa Aesar; 97%) were dried over molecular sieves 4A 1/16 before use. Distilled deionized water was used as a form of saturated solution in toluene ([H_2O] = 22 mM at 20 °C).[14] Carbon tetrachloride (an internal standard for gas chromatography) was dried overnight over calcium chloride and distilled twice from calcium hydride. Me_2S (TCI; >99%) was dried overnight over calcium chloride and distilled from sodium. 1-Adamantanol (AdOH, Aldrich; 99%), 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (Glucopyranose, TCI; >95%), (1R,2S,5R)-(–)-menthol ((–)-Menthol, Aldrich; 99%), tricyclohexylmethanol (Cy_3MeOH, Aldrich; 97%), 1-pyrenemethanol (1-PyMeOH, Aldrich; 98%), triphenylmethanol (TritylOH, Aldrich; 97%), 9-phenyl-9-fluorenol (Fluorenol, Aldrich; 99%), and 3'-hydroxyacetophenone (3AcPhOH, TCI; >98%) and 4'-hydroxyacetophenone (4AcPhOH, TCI; >98%), phenol (PhOH, Wako; 99%), 2,6-diphenylphenol ($(Ph)_2$PhOH, Aldrich; 98%), 2,6-diisopropylphenol ($(i\text{-Pr})_2$PhOH, TCI; >98%), 1,4-dithiane (DT, Aldrich; 97%), 1,4-thioxane (TO, Aldrich; 98%), and BF_3OEt_2 (Aldrich) were used as received. Toluene (solvent) was passed through purification column (Solvent Dispensing System; Glass Contour) before use.

Polymerization Procedure

Polymerization was carried out under dry nitrogen in baked glass tubes equipped with a three-way stopcock. A typical example for TBVE polymerization with MeOH/Me_2S/BF_3OEt_2 is given below: The reaction was initiated by adding solutions of BF_3OEt_2 (0.3 mL, as a 240 mM solution) in toluene via a dry syringe into a mixture (2.7 mL) of TBVE (0.39

mL) and CCl_4 (0.20 mL) containing MeOH and Me_2S in toluene at -78 °C. After a predetermined interval, the polymerization was terminated with prechilled methanol (1.2 mL) containing a small amount of ammonia. Monomer conversion was determined from its residual concentration measured by gas chromatography with CCl_4 as an internal standard. The quenched reaction mixture was washed with dilute hydrochloric acid, aqueous sodium hydroxide solution and water to remove initiator residues, evaporated to dryness under reduced pressure, and vacuum-dried to give the polymer.

Measurements

The M_n, M_w/M_n, and MWD curves of the polymers were determined by size-exclusion chromatography (SEC) in chloroform at 40 °C using three polystyrene gel columns [Shodex K-805L (pore size: 20-1000 A; 8.0 mm i.d. × 30 cm) × 3; flow rate 1.0 mL/min] that were connected to a Jasco PU-980 precision pump, a Jasco RI-930 refractive index detector. The columns were calibrated against 13 standard poly(styrene) samples (TOSOH; M_n = 500-3,840,000; M_w/M_n = 1.01-1.14). ^{13}C NMR spectra of produced polymers were recorded on a JEOL JNM-LA500 spectrometer in CCl_4/C_6D_6 (9/1) at 55 °C operating at 125.83 MHz (^{13}C). Polymer samples for NMR were fractionated by preparative SEC (column: Shodex K-5002F).

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PART II

Control of Terminal Structure

Chapter 3

Quantitative End-Capping with Alcohols: Terminal Umpolung with a Modifier Monomer in Living Radical Polymerization

Abstract

In this work, the author demonstrated a novel method for a quantitative substitution of terminal-halogen with alkoxy group in ruthenium-catalyzed living radical polymerization of methyl methacrylate (MMA), taking notice of that the leaving group is common with that in Lewis acid-catalyzed living cationic polymerization. The crucial point is a modification of the terminal carbon halogen bond to be polarized for an acceptance of ionic substitution by alcohol, which was brought about by attaching a "modifier monomer" with conjugated and electron-donating substituents, such as *p*-methoxystyrene (pMOS) and α-methoxystyrene (αMOS). This method would be developed for various functionalizations at terminal with use of the corresponding alcohols.

Introduction

For their precision control, most of "modern" living polymerizations, in principle, depend on dormant species, meta-stable covalent precursors that are incapable of propagation per se but effectively serve as reservoirs for true growth-active species upon catalysis. This is particularly true for transition metal-catalyzed living radical polymerization,[1] where halogen-capped polymers are dormant species to generate growing carbon radicals via transition metal catalysis, reversibly, dynamically, and selectively to ensure efficient propagation, while thermodynamically favored enough to maintain a sufficiently low intermediate concentration so as to suppress bimolecular termination and other side reactions inherent to conventional radical polymerization (eq. 1; X = halogen; R = ester):

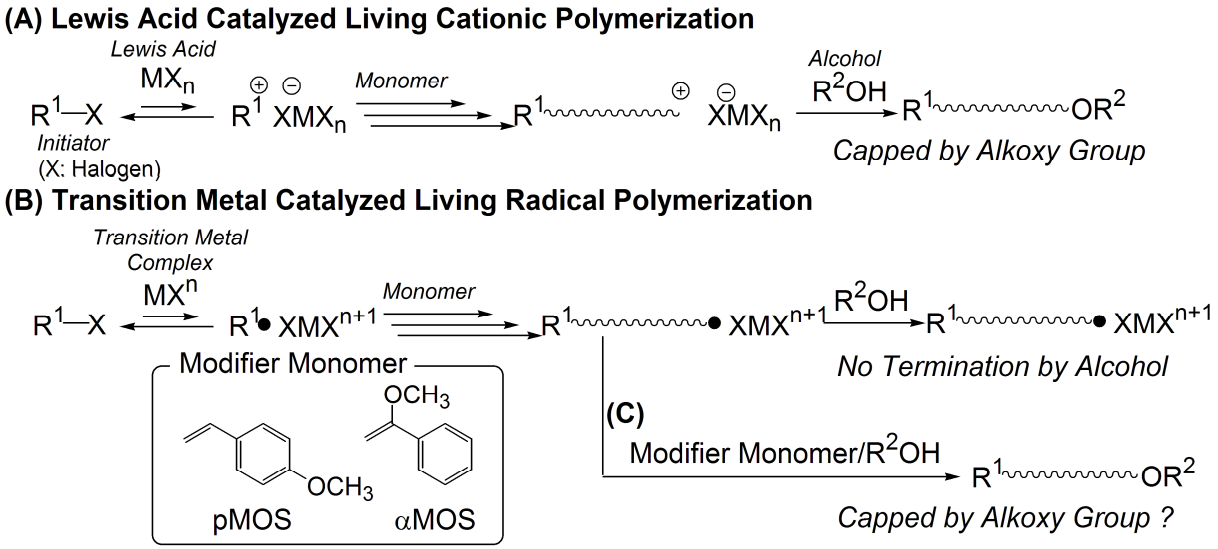
$$\sim\sim\sim CH_2\text{-}CHR\text{-}X \text{ (dormant)} \xrightarrow[\text{Reversible}]{\text{Metal Catalyst}} \sim\sim\sim CH_2\text{-}CHR \text{ (active radical)} \quad (1)$$

The fair stability of these alkyl halides imposes double-edged features, excellent for reaction control but excess for terminal functionalization. End-capping agents are indeed available, such as silyl enol ethers,[2] allyl compounds,[3] tin compounds,[4] and azides,[5] but in the author's view, all these seem neither universal nor satisfactory one way or another, either exotic, expensive, or inefficient. The primary reason is that the dormant halide terminal should carry a conjugating, radical-stabilizing substituent, typically an ester (R in eq. 1), that is in most cases also electron-withdrawing and thereby renders the halogen reluctant to ionically, albeit radically, dissociate and to undergo concerted nucleophilic or electrophilic substitution reactions. No doubt, efficient, selective, and quantitative terminal transformation has long been required, in part to eliminate the terminal halogen that potentially induce undesired reactions upon polymer processing and, more importantly, to expand the versatility in polymer synthesis directed to, for example, block, graft, telechelic, and other functionalized macromolecules.[6]

This work is to provide a novel method for an efficient transformation of the dormant species in metal-catalyzed living radical polymerization, taking notice that the terminal halogen is ambivalent and may be eligible not only to radical but also to ionic substitution depending on the electronic nature of its geminal substituent [R in $\sim\sim\sim CH_2$–CHR-X] (eq. 1). In this regard the author is particularly interested in "umpolung"[7] (unpoling) of the alkyl halide by replacing the original ester substituent (R) with a methoxy group, which may stabilize a radical through a mild conjugation and may simultaneously activate the precursor

halide towards cationic dissociation (or electrophilic substitution), just as in the Lewis acid-catalyzed living cationic polymerization discovered by Higashimura, Sawamoto and co-workers (Scheme 1, A).[8] For the umpolung the author herein employs a "modifier monomer", an alkene suited for not only radical but also cationic polymerizations as well (Scheme 1, B). Namely, a modifier monomer should effectively add to a growing radical to form an "umpoled" dormant end that should be available for electrophilic substitution. The newly formed terminal now carries a halogen that is, in turn, readily substituted or quenched with suitable nucleophiles like an alcohol, as Sawamoto et al. have already demonstrated.[8]

As illustrated more specifically in Scheme 1, the author herein employed *p*-methoxystyrene (pMOS) and *α*-methoxystyrene (αMOS) as modifier monomers with an alkoxy group. These alkenes are active enough to react with the growing radicals due to the conjugated phenyl group, and the resulting alkoxystyryl halides may effectively be elctrophilically quenched with an alcohol due to the high electron-donating alkoxy group. Given a large variety of alcohols with additional functionality, design of the alcohol quenchers will open a new route to replace the potentially noxious terminal halogen with a more useful terminal function.



Scheme 1. Quantitative End-Capping with Alcohols in Living Polymerization

Results and Discussion

1. Living Radical Polymerization.

Methyl methacrylate (MMA) was polymerized with a ruthenium complex [Ru(Ind)Cl(PPh_3)$_2$, Ind = η^5-C_9H_7; RuCl(Ind)][9] as a catalyst in conjunction with ethyl 2-chloro-2-phenylacetate (ECPA; initiator)[10] and *n*-Bu_3N (cocatalyst or additive)[11] in toluene at 80 °C. Within 13 h, the MMA conversion reached 33 %, and controlled polymers (PMMA) were obtained: the number-average molecular weight was close to the theoretical value (M_n = 4,300 vs. $M_{theo.}$ = 3,500; the former by size-exclusion chromatography, SEC; the latter based on $[MMA]_0/[initiator]_0$); and the molecular weight distribution (MWD) was narrow (M_w/M_n = 1.25) (Figurer 1A-1). The fine controllability was also shown by structural analysis by MALDI-TOF-MS (Figure 1B-1) and ^{1}H-NMR (Figure 2A). Specifically important in this work is that these observations demonstrate the selective and quantitative formation of a chlorine-capped terminal originating from the initiator [$F_n(\alpha)$ = 1.0; $F_n(\omega)$ = 0.95; by ^{1}H-NMR].

2. Terminal "Umpolung" with Modifier Monomer pMOS.

The polymerization solution, thus obtained at a 33 % conversion, was evaporated under an inert and air-free atmosphere to remove the remaining MMA.[12] The reaction mixture now consisted of the Cl-capped PMMA, the ruthenium catalyst, and *n*-Bu_3N, [13] with toluene and *n*-octane (internal standard for gas chromatography) removed. To this mixture was added pMOS (10 eq to PMMA or the terminal chlorine), excess methanol (MeOH; 8 vol%) and toluene (84 vol%), and the solution was heated at 80˚C for 8 h. Upon a dual mode-detection SEC analysis, the isolated products (Figure 1A-3) exhibited an intense UV response at 250 nm that was virtually absent in a control product (Figure 1A-2) obtained under the same conditions but without pMOS treatment, while both samples had nearly identical narrow and unimodal MWDs under refractive-index (RI) detection. These results show that a pMOS unit(s) was introduced into the PMMA terminal without further propagation and undesirable side reactions.

The terminally modified products were further analyzed by MALDI-TOF-MS[14] (Figure 1B, 1–3). The peak pattern was quite different from that for the corresponding controls, PMMAs one directly obtained just after the living radical polymerization and the other treated with MeOH alone (traces 3 vs. 1 and 2). The spectrum for the modified

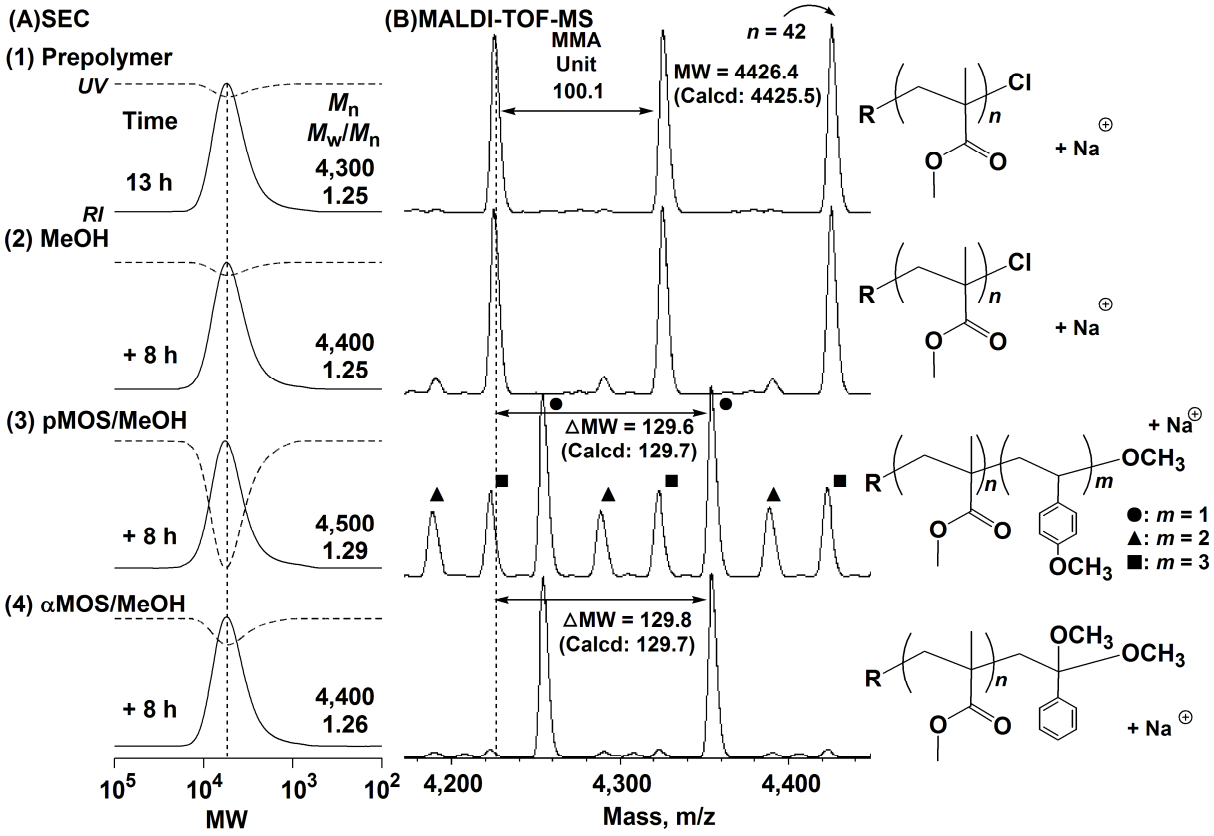


Figure 1. (A) SEC curves and (B) MALDI-TOF-MS spectra of PMMA obtained with ruthenium-catalyzed living radical polymerization and sequential end-capping reaction with a modifier monomer and methanol in toluene at 80 ˚C: Polymerization, $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[n\text{-}Bu_3N]_0$ = 20 mM; End-capping reaction, $[Modifier\ Monomer]_{add}$ = 200 mM; $[MeOH]_{add}$ = 2.0 M; $[n\text{-}Bu_3N]_{add}$ = 20 mM. (1) Polymerization in 13h; (2) Control experiment for end-capping without a modifier monomer; (3) End-capping with pMOS; (4) End-capping with αMOS. Reaction time for end-capping is 8 h.

products (Figure 1B-3) consisted of one major (with circles) and two minor series (with triangles and squares) of peaks, all separated by the 100.1 mass unit of MMA and the major series turned out to be separated from the chlorine-capped PMMA series by a mass unit of 129.6, close to the value (129.7) for a single pMOS unit with a methoxy terminal but without a chlorine, as indicated in trace 3 [~~~$(MMA)_n$–$(pMOS)_m$–OCH_3; m = 1]. The main array was further separated from another minor series (with triangles) by a mass difference indicative of the same structure but doubled pMOS units (m = 2). These results therefore show the formation of PMMA carrying an extended short segment with one and two (and possibly three) pMOS units and also capped with a methoxy group from MeOH. The conclusion was corroborated by ^{1}H-NMR analysis. The peak for a terminal MMA-chlorine

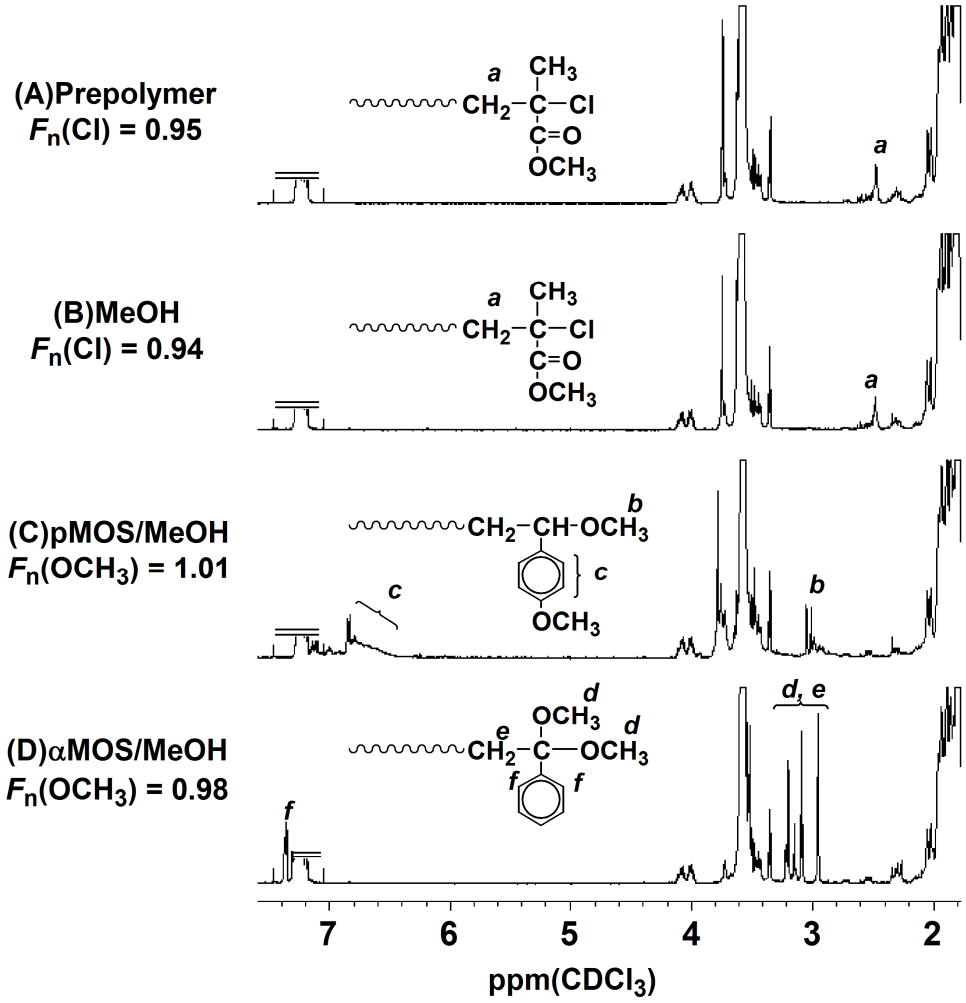


Figure 2. ^{1}H NMR spectra of PMMA obtained with ruthenium-catalyzed living radical polymerization and sequential end-capping reaction with a modifier monomer and methanol in toluene at 80 ˚C: Polymerization, $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[nBu_3N]_0$ = 20 mM; End-capping reaction, [Modifier Monomer]$_{add}$ = 200 mM; $[MeOH]_{add}$ = 2.0 M; $[nBu_3N]_{add}$ = 20 mM. (A) Polymerization in 13h; (B) Control experiment for end-capping without a modifier monomer; (C) End-capping with pMOS; (D) End-capping with αMOS. Reaction time for end-capping is 8 h; F_n is calculated from M_n(SEC)/M_n(NMR).

(*a*, 2.5 ppm) was replaced with new peaks assignable to pMOS unit(s) (*c*, 6.5–6.9 ppm) and to a methoxy terminal (*b*, 3.0 ppm). The peak intensity ratios, based on the aromatic protons, further indicated the attachment of average 1.2 pMOS units per chain (Figure 2C).

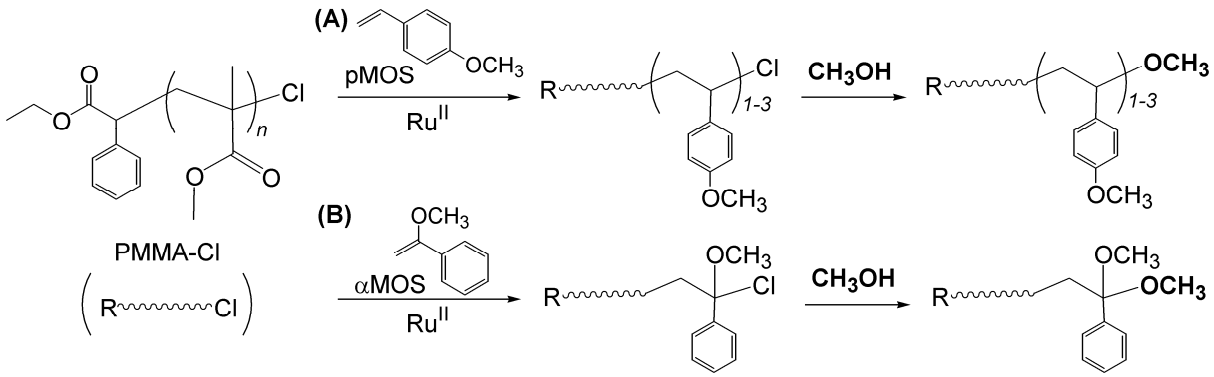
Thus, a few pMOS monomers polymerized from the Cl-capped dormant PMMA, radically under the ruthenium catalysis, to form a new chloride terminal now attached to a pMOS unit and was thereby umpoled and activated to readily react with added MeOH to eventually give a methoxy terminal (Scheme 2A). The results therefore demonstrate that

the author's "umpolung" strategy works but that the use of pMOS as a modifier monomer is not perfectly suited, albeit effective, by giving mixed products with varying length of the terminal pMOS segments.

3. Terminal "Umpolung" with Modifier Monomer αMOS.

In an effort to obtain a more uniform structure of the methoxy-capped polymer, the author employed an α-substituted methoxystyrene (αMOS) in place of pMOS as a modifier monomer, because αMOS, a sterically hindered α,α-disubstituted alkene, is less favorable for radical polymerization.[15] Upon a treatment identical with the procedures with pMOS except for the use of αMOS, the products led to SEC traces with weaker UV-intensity, consistent with an αMOS-capped structure with a weaker aromatic chromophore (Figure 1A-4). A single peak-series with the MMA mass difference was observed in MALDI-TOF-MS spectrum (Figure 1B-4). The observed absolute mass values agreed with the calculated ones for the expected structure with a single αMOS unit and a methoxy terminal (from MeOH) attached to a PMMA chain. Thus, the author achieved quantitative methoxy-capping for one series of PMMA (Scheme 2B).

Such a selective methoxy-capping via a single αMOS extension was also possible even when a mixture of αMOS and MeOH was directly added into a polymerization solution without the evaporation of remaining MMA. This result will be reported in the Chapter 4.



Scheme 2. End-Capping via Terminal Umpolung with a Modifier Monomer

Conclusion

The author demonstrated a novel method for a quantitative substitution of terminal-halogen in PMMA obtained with ruthenium-catalyzed living radical polymerization. The crucial point is a modification of the terminal carbon halogen bond to be polarized for an acceptance of ionic substitution by alcohol, which was brought about by attaching a modifier monomer with conjugated and electron-donating substituents, such as pMOS and αMOS. This method would be developed for various functionalizations at terminal with use of the corresponding alcohols.

Experimental Section

Materials

MMA (Tokyo Kasei; purity > 99%) was dried overnight over calcium chloride and distilled twice from calcium hydride under reduced pressure before use. Ethyl 2-chloro-2-phenylacetate (ECPA, Aldrich; >97%) was distilled under reduced pressure before use. $Ru(Ind)Cl(PPh_3)_2$ (Strem) was used as received and handled in a glove box under a moisture- and oxygen-free argon atmosphere (H_2O < 1 ppm, O_2 < 1 ppm). *n*-Bu_3N (Tokyo Kasei; >99%) was bubbled with dry nitrogen for more than 15 min before use. *n*-Octane (internal standard for gas chromatography for MMA) was dried overnight over calcium chloride and purified by double distillation from calcium hydride before use. Toluene (solvent) was passed through purification column (Solvent Dispensing System; Glass Contour) before use. *p*-Methoxystyrene (pMOS, Aldrich; >97%) was washed with 10 % aqueous sodium hydroxide and then with saturated aqueous sodium chloride, dried overnight over sodium sulfate, and distilled under reduced pressure before use. *α*-Methoxystyrene (αMOS) was prepared according to the literature.[16] Methanol (Wako, dehydrated) was degassed before use.

Polymerization and End-Capping Reaction

The polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock. A typical procedure for polymerization of MMA with ECPA/$Ru(Ind)Cl(PPh_3)_2$/*n*-Bu_3N and sequential end-capping reaction with

pMOS/methanol is given below: In a glass tube was placed Ru(Ind)Cl(PPh_3)$_2$ (0.01 mmol, 7.76 mg), and toluene (3.45 mL), *n*-octane (0.13 mL), solutions of *n*-Bu_3N (0.25 mL of 400 mM in toluene, 0.1 mmol), MMA (1.07 mL, 10 mmol) and solutions of ECPA (0.10 mL of 995.8 mM in toluene, 0.1 mmol) were added sequentially in this order at room temperature under dry argon. The total volume of the reaction mixture was thus 5.0 mL. Immediately after mixing, the mixture was placed in an oil bath kept at 80 °C. After the polymerization had reached 33% conversion in 13 h, the polymerization solution was evaporated to remove the residual monomer, followed by the addition of toluene (4.21 mL), solutions of *n*-Bu_3N (0.25 mL of 400 mM in toluene, 0.1 mmol), methanol (0.41 mL, 10 mmol) and pMOS (0.13 mL, 1.0 mmol). Monomer conversion was determined from the concentration of residual monomer measured by gas chromatography with *n*-octane as an internal standard. In predetermined intervals, part of the solution was sampled and terminated by cooling in -78°C to pursue the reaction. The quenched reaction solutions were evaporated to dryness to give the products, which were subsequently vacuum-dried overnight.

Measurements

The M_n, M_w/M_n, and MWD curves of the polymers were determined by size-exclusion chromatography in chloroform at 40 °C using three polystyrene gel columns [Shodex K-805L (pore size: 20-1000 A; 8.0 mm i.d. × 30 cm) × 3; flow rate 1.0 mL/min] that were connected to a Jasco PU-980 precision pump, a Jasco RI-930 refractive index detector, and a Jasco UV/vis detector set at 250 nm. The columns were calibrated against 12 standard poly(MMA) samples (Polymer Laboratories; M_n = 630-1,200,000; M_w/M_n = 1.06-1.22) as well as the monomer. ^{1}H NMR spectra were recorded in $CDCl_3$ at room temperature on a JEOL JNM-LA500 spectrometer, operating at 500.16 MHz. Polymer samples for ^{1}H NMR were fractionated by preparative SEC (column: Shodex K-5002F). MALDI-TOF-MS analysis was performed on a Shimadzu AXIMA-CFR instrument equipped with 1.2 m linear flight tubes and a 337 nm nitrogen laser with dithranol (1,8,9-anthracenetriol) as an ionizing matrix and sodium trifluoroacetate as a cationizing agent.

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(12) The author also examined direct addition of a pMOS/MeOH mixture without the evaporation-procedure described in the text. However, the more the MMA residue, the more pMOS was needed for the modification, which in turn resulted in higher polymeric by-products most likely due to spontaneous radical polymerization of pMOS.

(13) Note that the amine cocatalyst remaining in the mixture now serves as a base (proton trap) in the methoxy-capping.

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Chapter 4

End-Functionalization with Alcohols: Various End-Functionalized Polymers through Umpolung in Living Radical Polymerization

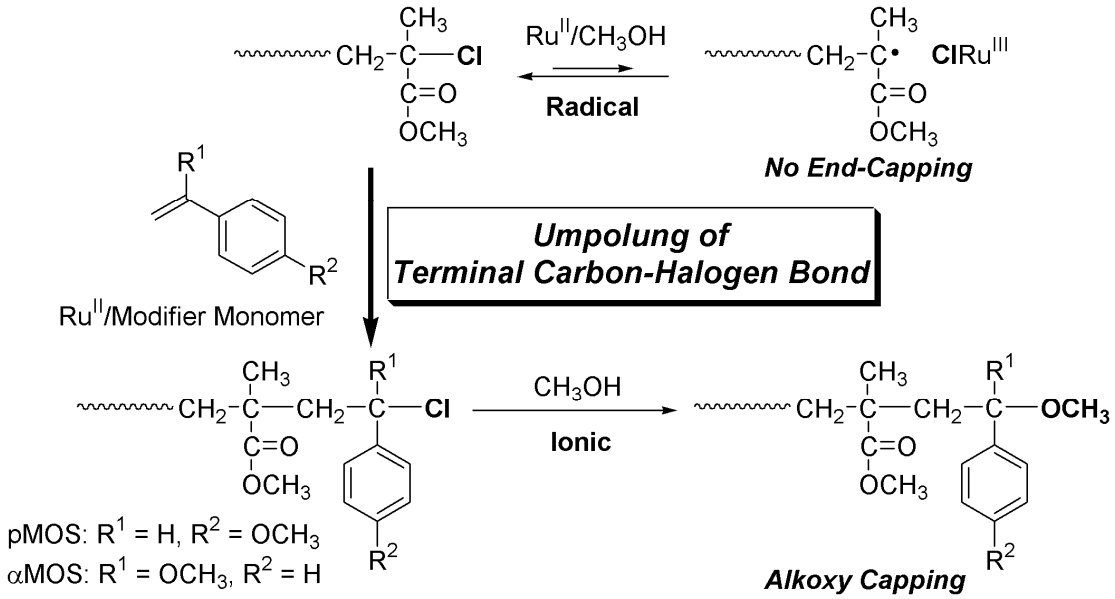
Abstract

A novel method is described for the synthesis of end-functionalized polymers [–C–OR; R = CH_2CH_2OH, $(CH_2)_3CH=CH_2$; $CH_2C(O)C_6H_5$] via sequential terminal "umpolung" and alkoxy end-capping in metal-catalyzed living radical polymerizations of methyl acrylate and methacrylate with Ru(II) catalysts. The first umpolung step involved the single-unit addition of a "modifier monomer" [$CH_2=C(OCH_3)C_6H_5$; αMOS] onto the growing carbon-halogen end (~~C–X; X = Cl, Br) to modify it from neutral (radical) into more nucleophilic (carbocationic). Subsequently, the modified terminal was quantitatively end-capped into an alkoxy with a functionalized alcohol (ROH). Systematic evaluation indicated that the "modifier monomer" be bulky (geminally disubstituted) and thus incapable of homopropagation and be electron-rich and conjugated for promoting the subsequent electrophilic substitution of alcohols. Thus, *α*-methoxystyrene (αMOS) was better suited than its *α*-monosubstituted *p*-methoxy and *α*-methyl-*p*-methoxy versions, with which respectively homopropagation overrode the single addition and HX elimination occurred over the alcoholic substitution. For the second step a variety of functionalized alcohols are available; the simple methoxy from methanol may further be reduced into a more versatile ketone functionality. Similarly, telechelic polymers were also obtained from α,ω-bifunctional polymers.

Introduction

End-functionalized polymers are versatile in synthetic applications such as surface modification, sealing (as sealants), block copolymer synthesis, and, most recently, bioconjugaion.[1] They are usually prepared by living polymerization, either by initiation or by end-capping, or both (into telechelics). Functionalized initiators and terminators (end-capping agents) have thus been developed, but in living radical polymerization, the neutrality of intermediate radicals renders quantitative end-capping relatively difficult, with the scope of end-cappers thus limited. This problem is especially true for metal-catalyzed systems involving dormant species where the carbon–halogen terminal is covalent, highly stable, less polarized, and thereby less suitable for end-capping via substitution.[2] To date, few methods have been reported for radical end-capping: silyl enol ethers for ketones,[3] tin compounds for hydrogenation and allylation,[4] allyl compounds for hydroxyl and epoxide groups,[4b,5] and sodium azides for "click" reactions;[6] and these are not free from problems and limitations in terms of readily available end-functionality and sometimes safety.

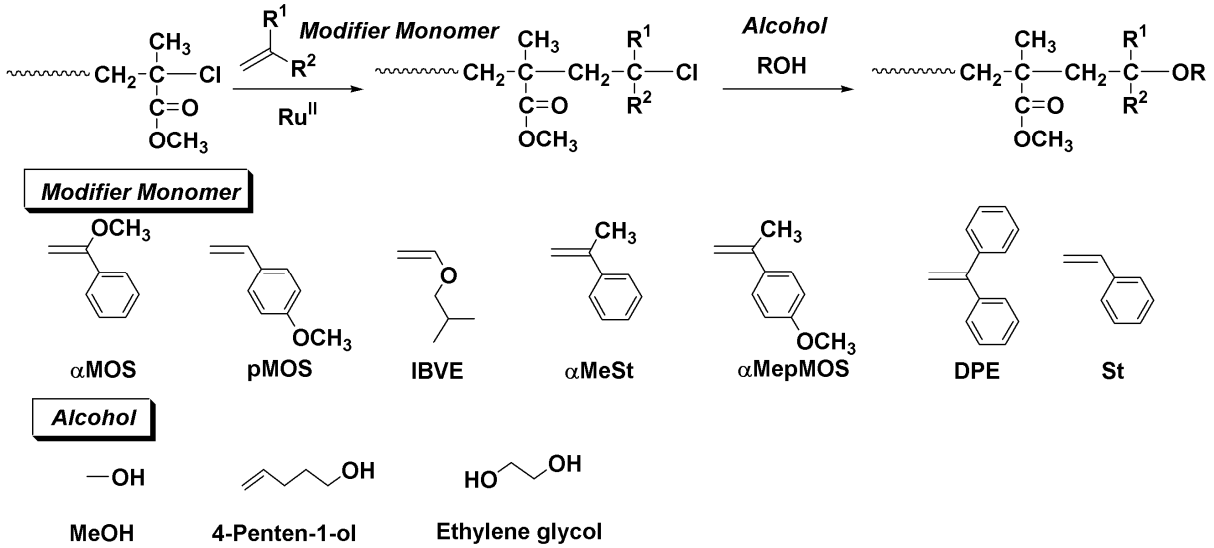
As shown in Chapter 3,theauthor has recently developed a versatile end-capping method to quantitatively convert a dormant halogen terminal into other functional groups in the metal-catalyzed living radical polymerization of methyl methacrylate (MMA),[7] in which the rather unreactive –MMA–Cl terminal may be converted into an electrophilically more reactive –MMA-(alkoxystyrene)-Cl end (Scheme 1).[8] The crucial point is *umpolung*[9] of the



Scheme 1. Umpolung of Terminal Carbon–Halogen Bond with a Modifier Monomer

terminal carbon–halogen bond via the addition of a "modifier monomer", such as *p*-methoxystyrene (pMOS) or *α*-methoxystyrene (αMOS), that carries a highly electron-donating as well as conjugating pendent group. Thus, the *α*-substituent adjacent to the terminal carbon-halogen linkage is converted in-situ from electron-withdrawing into electron-donating so as to be accessible to nucleophilic reagents; most typically, an MMA ester into an αMOS alkoxyphenyl for alcohol end-capping into an alkoxy (acetal) terminal. Obviously, the design criteria for the modifier monomer involve the selection of an ambivalent umpolung group, as with the *p*- or α-alkoxyphenyl group, that is conjugating for radical addition and electron-donating for the subsequest nucleophilic substitution.

In this chapter, the author examined the utility and scope of this umpolung end-capping methodology for the ruthenium(II)-catalyzed living radical polymerization (Scheme 2). The author first employed various monomers as potential *umpolung* end-group modifiers to examine the effects of their structure on this end-functionalization. Second, the author employed various functionalized alcohols for synthetically attractive end-functionalization. As a result, a non-conjugated olefin and a hydroxy group were quantitatively introduced onto the poly(MMA) terminal through the sequential addition of αMOS (modifier) and a functionalized alcohol (i.e., 4-penten-1-ol and ethylene glycol, respectively). A ketone terminal was also obtained from the acetal derivative, derived from the αMOS/methanol combination, via a simple acid treatment.



Scheme 2. Umpolung of Terminal Carbon–Halogen Bond toward End-Functionalization

Results and Discussion

1. Design of Modifier Monomers.

The author examined a series of vinyl compounds as potential modifier monomers for the ruthenium-catalyzed living radical polymerization of MMA, followed by end-capping with methanol. As discussed in the Introduction, the selection criteria included: (a) the quantitative and possibly single-unit addition to the living poly(MMA) end and (b) the fast and quantitative termination with methanol to give a methoxy-capped polymer. Two samples of prepolymers were first prepared by the MMA polymerizations with a ruthenium catalyst [Ru(Ind)Cl(PPh_3)$_2$, Ind = η^5-C_9H_7],[10] in conjunction with a chloride initiator (ECPA)[11] and an amine cocatalyst (*n*-Bu_3N)[12] in toluene at 80 °C, where conversion reached 30–40% in 13 h (Figure 1, A and F). For both samples, the terminal group was chlorine (Cl) with an almost quantitative functionality [$F_n(\omega) > 0.95$ by ^{1}H NMR], indicating the polymerizations were well controlled.[13]

The polymerization solutions were then evaporated under an inert and air-free atmosphere to remove the remaining MMA. To the as-obtained residues were added, sequentially, an excess of a modifier monomer (10 molar equivalents to the prepolymer), excess methanol (100 eq), *n*-Bu_3N (to be 40 mM after addition) and toluene, and the solution was heated and kept at 80 ˚C for an additional 8 h. The resultant polymers were analyzed by SEC (with RI and UV detectors, Figure 1), MALDI-TOF-MS (Figure 2), and ^{1}H NMR.[7] As already reported, the reactions with αMOS or pMOS induced a quantitative methoxy-capping (B and C, respectively, both in Figures 1 and 2; $F_{n,\,methoxy} > 0.98$ by ^{1}H NMR).[7] With the *α*- or *p*-methoxy substituent, the electron-rich and highly reactive radical species derived from these modifiers thus led to the effective cationic end-capping with the methoxy group from added methanol. Note that the quantitative and selective single-unit addition took place with αMOS, whereas the addition was multiple with pMOS, thus the former is among the best end-group modifiers (see below).

In contrast, few end-capping reactions occurred with isobutyl vinyl ether (IBVE) (D in both Figures 1 and 2; $F_{n,\,methoxy} \sim 0.15$ by ^{1}H NMR), most likely because IBVE is indeed electron-donating but non-conjugating ($e = -1.27$; $Q = 0.030$) and thus inefficient in radical addition.[14] With *α*-methylstyrene derivatives (i.e., *α*MeSt and *α*MepMOS), both electron-donating and conjugating, therefore, the expected addition did proceed, as indicated by the SEC curves of the products where UV response (250 nm) sharply increased while peak

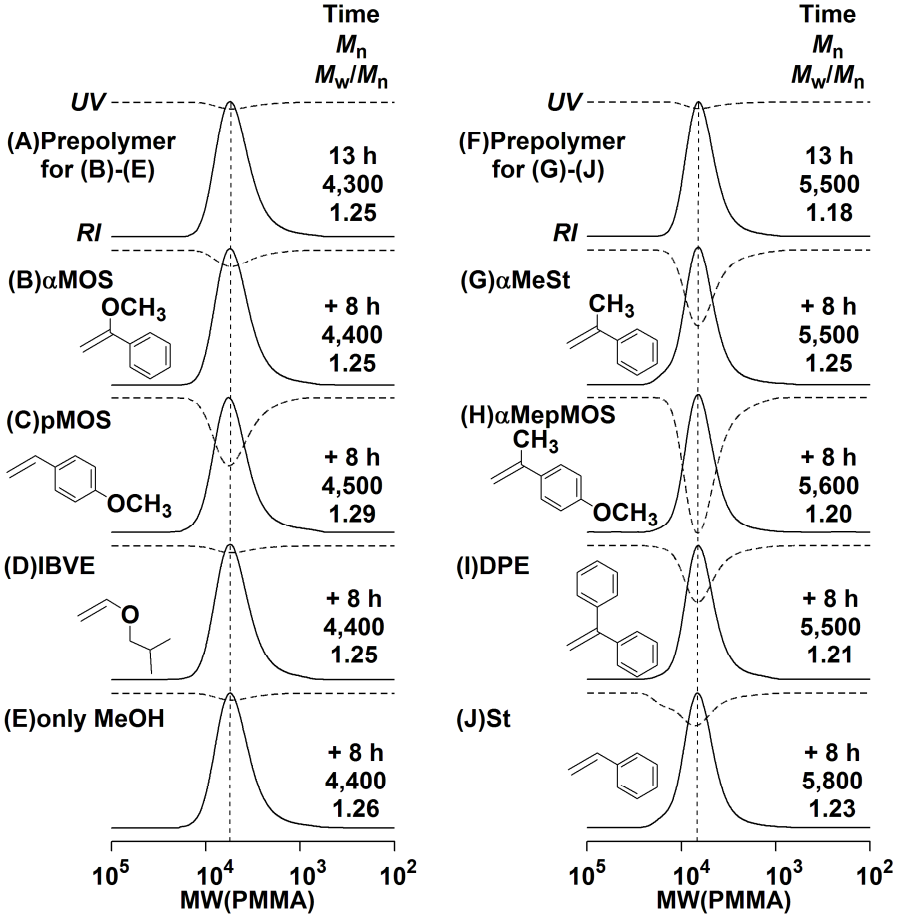


Figure 1. SEC curves of PMMAs obtained with ruthenium-catalyzed living radical polymerization (samples A and F) and subsequent sequential end-capping reactions with a modifier monomer and methanol in toluene at 80 ˚C (samples B–E from the prepolymer A and samples G–J from F). Polymerization conditions for samples A and F: $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[n\text{-}Bu_3N]_0$ = 20 mM; for 13 h; conversion 30-40%.[13] End-capping reactions for samples B–E and G–J: $[\text{modifier monomer}]_{add}$ = 200 mM; $[MeOH]_{add}$ = 2.0 M; $[n\text{-}Bu_3N]_{add}$ = 20 mM (additionally applied upon the modifier addition); modifier addition at 13 h; end-capping for an additional 8 h. Modifier: (B) αMOS; (C) pMOS; (D) IBVE; (E) none (control experiment); (G) αMeSt; (H) αMepMOS; (I) DPE; (J) St.

positions little shifted (Figure 1, G and H). However, MALDI-TOF-MS and ^{1}H NMR analysis revealed that the main terminals were not the expected methoxy by methanol-quenching [$F_{n,\ methoxy}$ ~ 0.06 (αMeSt), 0.34 (αMepMOS) by ^{1}H NMR] but an exo-olefin by the proton-elimination from the terminal α-methyl (Figure 2, G and H). These monomers indeed added radically to the PMMA terminal, but the resulting terminals seemed so unstable that, upon treatment with methanol, HCl-elimination occurred in preference to methoxy-capping.[3b,15]

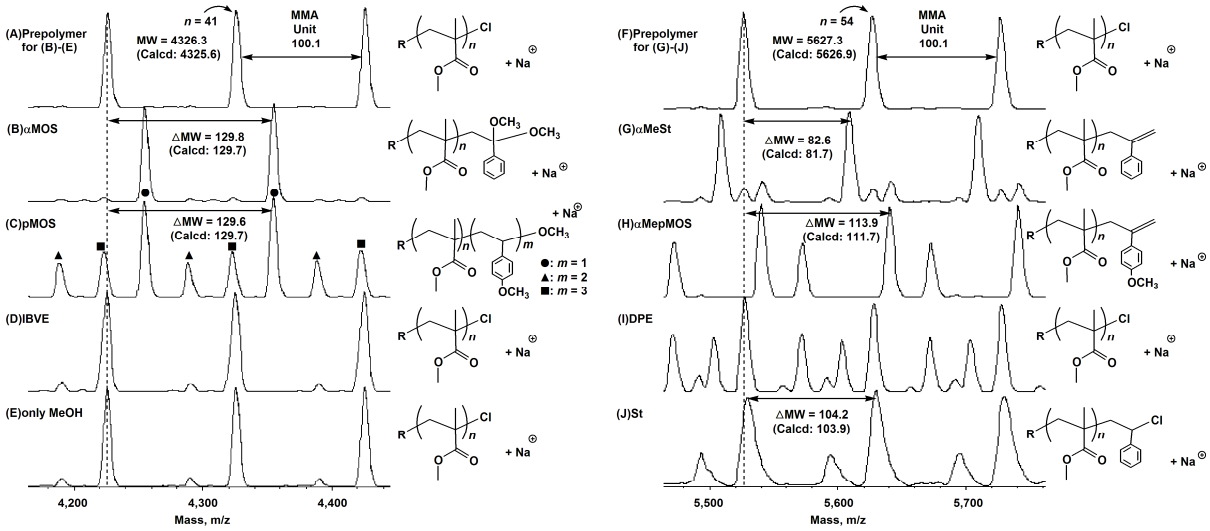


Figure 2. MALDI-TOF-MS spectra of PMMAs. See Figure 1 for the reaction conditions. The chemical drawings represent polymer structures characterized by masses of series peaks (only main products).

In consideration of these facts, 1,1-diphenylethylene (DPE) was employed, which is geminally α-disubstituted but would be immune to such elimination. However, DPE almost failed to add onto the PMMA terminal and the main series of MALDI-TOF-MS peaks was identical to that of the precursor (Figure 2I; $F_{\mathrm{n,\ methoxy}} \sim 0.27$ by ^{1}H NMR). With styrene, a mono-substituted version of DPE, on the other hand, the SEC profile consisted of not only an enhanced UV peak but an additional shoulder in the higher molecular weight region (Figure 1J). This would indicate that a styrene unit was introduced at the PMMA terminal, but a small part of the resultant less stable styryl radical would have undergone bimolecular radical–coupling. Also, the terminal turned out to be primarily a Cl-capped styrene unit, according to MALDI-TOF-MS analysis, and thus no methoxy group was introduced at all. Presumably, the electron donacity of the styrene's phenyl group (e = –0.80) is not high enough for the ionic substitution with methanol.[14]

From these results, pMOS and αMOS proved to be suitable as a modifier monomer for poly(MMA), and especially αMOS gives well-defined end structures consisting of one unit of αMOS capped with a methoxy group.[7] Furthermore, these results verify the proposed umpolung mechanism (Scheme 2) with the modifier monomers, electron-donating, conjugating, and free from proton elimination nor other side-reactions.

2. End-Functionalized Polymers.

(a) Olefin and Hydroxyl Groups. For the end-capping after the umpolung, a variety of alcohols were employed in place of methanol to introduce a functional group at the terminal, coupled with *α*MOS as a modifier monomer. For an olefin or a hydroxyl terminal, 4-penten-1-ol or ethylene glycol, respectively, together with *α*MOS was added into a solution of living PMMA at a ca. 40% conversion, and the mixtures were stirred for 8 h; just prior to alcohol addition, the remaining MMA monomer was removed by evaporation.[7] The resultant polymers were then characterized by SEC and MALDI-TOF-MS (Figure 3). With both alcohols, the products showed SEC-RI traces just slightly shifting toward high MW region with narrow molecular weight distributions (MWDs) (M_w/M_n < 1.25), and intensified UV responses indicated the attachment of terminal *α*MOS units. MALDI analysis clearly demonstrated almost quantitative introduction of the added alcohol (alkoxy) residues carrying an olefin or a hydroxyl group beyond a single unit of *α*MOS ($F_{n,\,alkoxy}$ > 0.90 by ^{1}H NMR).

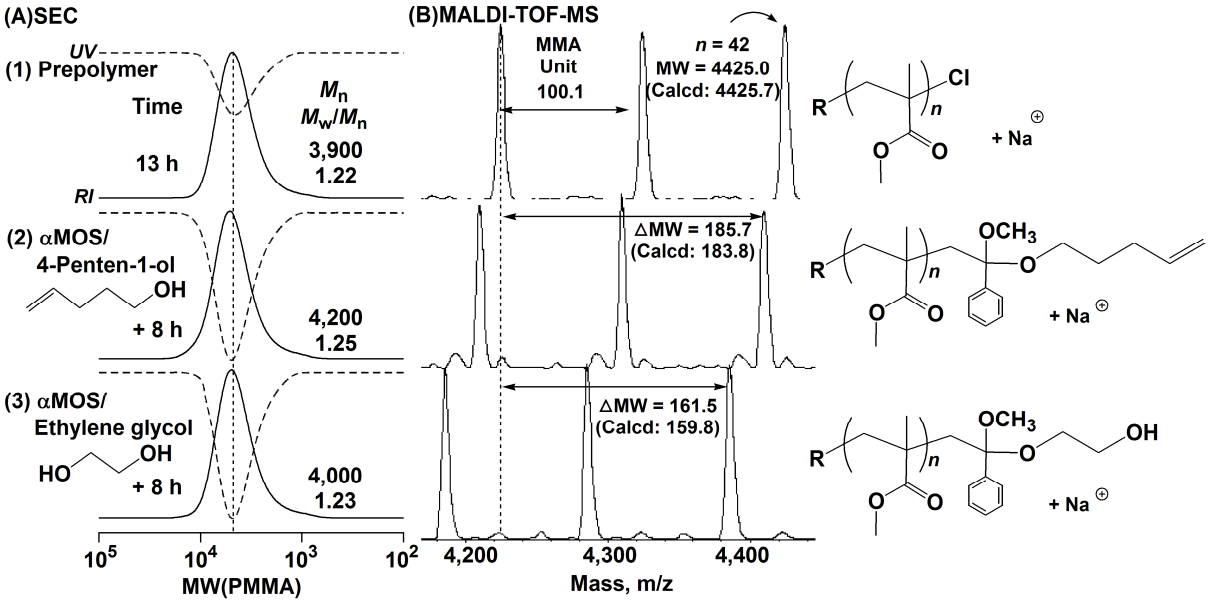


Figure 3. Structural analyses with (A) SEC curves and (B) MALDI-TOF-MS spectra for end-functionalization using 4-penten-1-ol (olefin) and ethylene glycol (hydroxyl). (1) Prepolymer PMMA (polymerization in 13 h). (2) End-capping with αMOS and 4-penten-1-ol. (3) End capping with αMOS and ethylene glycol. Polymerization: $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[n\text{-}Bu_3N]_0$ = 20 mM. End-capping reaction: $[\alpha MOS]_{add}$ = 200 mM; $[alcohol]_{add}$ = 2.0 M; $[n\text{-}Bu_3N]_{add}$ = 20 mM. Reaction time for end capping is 8 h.

(b) Ketone. The acetal terminal derived from the umpolung and end-capping with αMOS and methanol may also be converted into a ketone, another highly versatile terminal reactive

enough for further functionalization or conjugation with other molecules. For example, upon simple acid treatment, the SEC curve of the resultant polymer was almost the same as that of the pristine sample, while all the MALDI peaks shifted to lower mass by m/z ~ 46, in consistent with the quantitative conversion of the acetal to the corresponding ketone [$–CH_2$-$C(C_6H_5)(OCH_3)_2$ --> $–CH_2$-$C(C_6H_5)$=O] (Figure 4). Note that the acid treatment was carried out under so mild conditions that no side reactions occurred, such as degradation of the PMMA pendent esters.

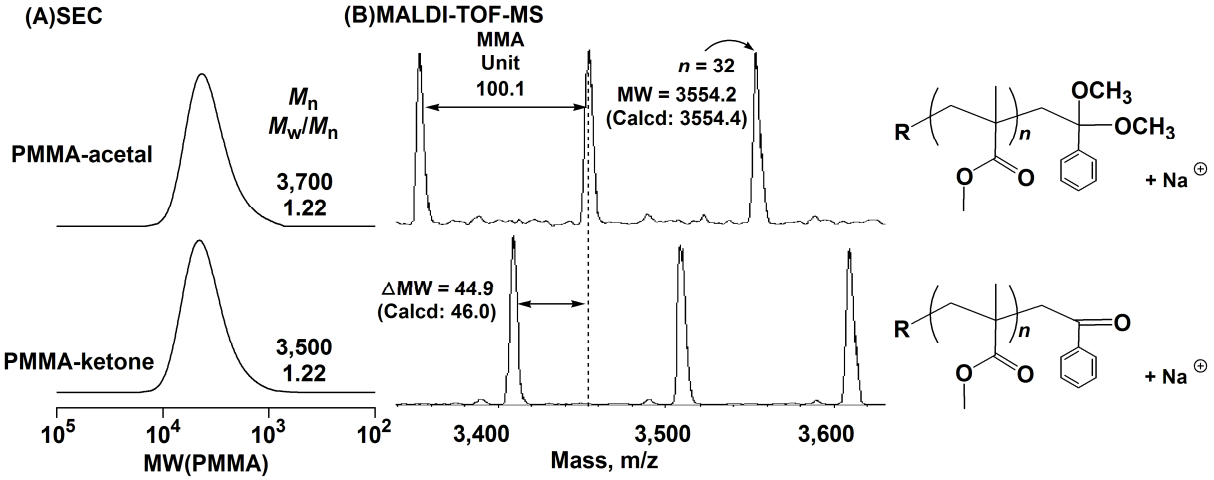


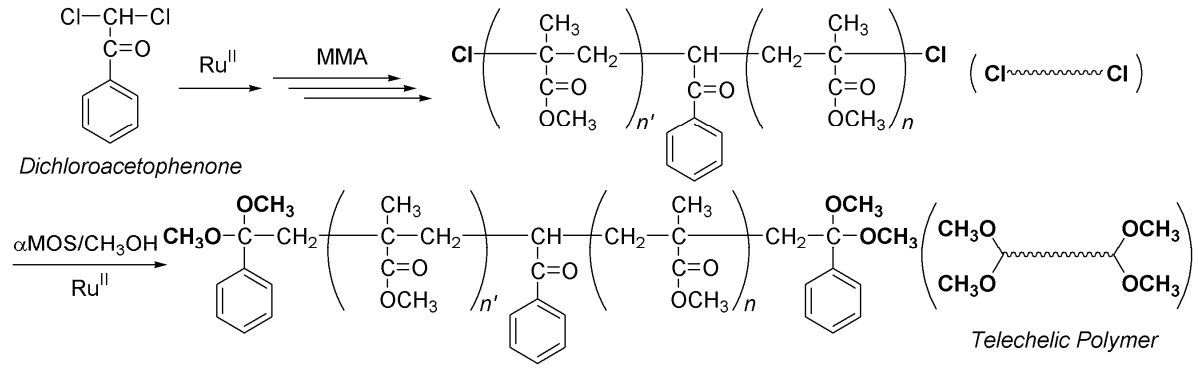
Figure 4. Structural analyses with (A) SEC curves and (B) MALDI-TOF-MS spectra for terminal conversion from acetal (PMMA-acetal: upper) to ketone (PMMA-ketone: lower) by the acidic treatment. See Figure 1 for the MMA polymerization with the ruthenium catalyst and the end-capping reaction with αMOS and methanol. Conversion from acetal to ketone: PMMA-acetal = 0.008 mmol in $CHCl_3/HCl_{aq}$ (9/1, v/v) at r. t. for 24 h, followed by evaporation.

3. Telechelic Polymers.

When combined with a bifunctional initiator, 2,2-dichloroacetophenone,[16] the αMOS/methanol end-capping led to telechelic polymers with methoxy (acetal) terminals (Scheme 3). The produced PMMAs were well controlled before and after the capping treatment (M_w/M_n = 1.22 and 1.25, respectively), and MALDI and ^{1}H NMR analysis verified the desired telechelic architecture, with an average end-functionality ~1.90 (Figure 5).

4. Direct Addition of Modifier Monomer and Alcohol without Residual MMA Removal.

In the above-described procedures, residual MMA (ca. 40% conversion) should be removed by evaporation prior to the addition of the modifier monomer and an alcohol, to



Scheme 3. Synthesis of Telechelic PMMA with a Bifunctional Initiator

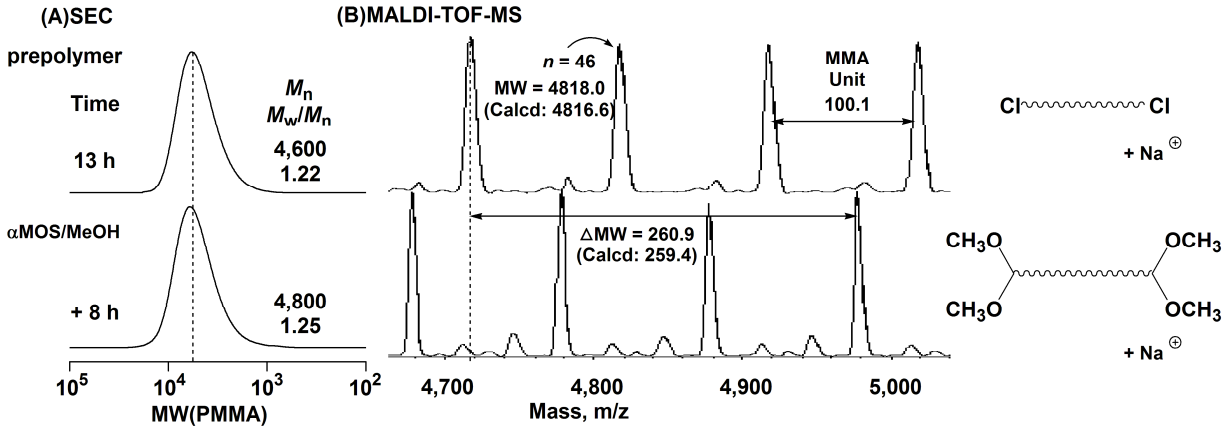


Figure 5. Structural analyses with (A) SEC curves and (B) MALDI-TOF-MS spectra for end-capping reaction of telechelic PMMA obtained with a bifunctional initiator under the ruthenium catalysis. Polymerization: $[MMA]_0$ = 2.0 M; [2,2-dichloroacetophenone]$_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; [*n*-$Bu_3N]_0$ = 20 mM in toluene at 80 ˚C. Polymerization time is 13 h (conversion: 51%). End-capping reaction: $[\alpha MOS]_{add}$ = 400 mM; $[MeOH]_{add}$ = 4.0 M; [*n*-$Bu_3N]_{add}$ = 40 mM. Reaction time for end-capping is 8 h.

ensure the quantitative end-capping. Here, a direct umpolung and end-capping without the evaporation procedure was tested for a simpler and more practically feasible process.

MMA was polymerized with the $Ru(Ind)Cl(PPh_3)_2$-catalyzed system (with ECPA and *n*-Bu_3N) in toluene at 80 °C.[7] When conversion reached as high as around 90%, 10 eq (for the initiator) of αMOS and 100 eq of MeOH were directly added to the polymerization mixture (Figure 6). During the reaction for an additional 8 h, MMA conversion had hardly increased, and the desired capping reaction apparently proceeded. Namely, little change was detected in SEC molecular weights and MWD, with enhancement of the UV response, and the quantitative methoxy capping was confirmed by MALDI-TOF-MS (Figure 7) and ^{1}H NMR (Figure 8; $F_{n,\,methoxy} > 0.94$). The observed MALDI peak masses fairly agreed with that of

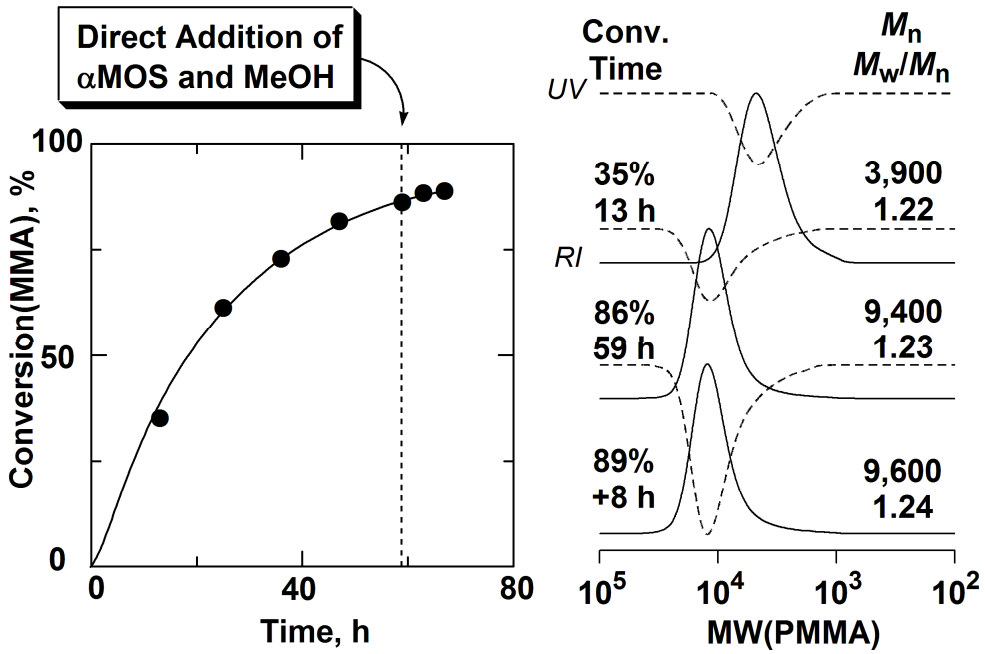


Figure 6. Time-conversion curve and SEC curves for direct end-capping reaction with αMOS/methanol for ruthenium-catalyzed living radical polymerization of MMA. Polymerization: $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[n\text{-}Bu_3N]_0$ = 20 mM. αMOS and methanol were added at 86% conversion: $[\alpha MOS]_{add}$ = 200 mM; $[MeOH]_{add}$ = 2.0 M. Reaction time for end-capping is additional 8 h.

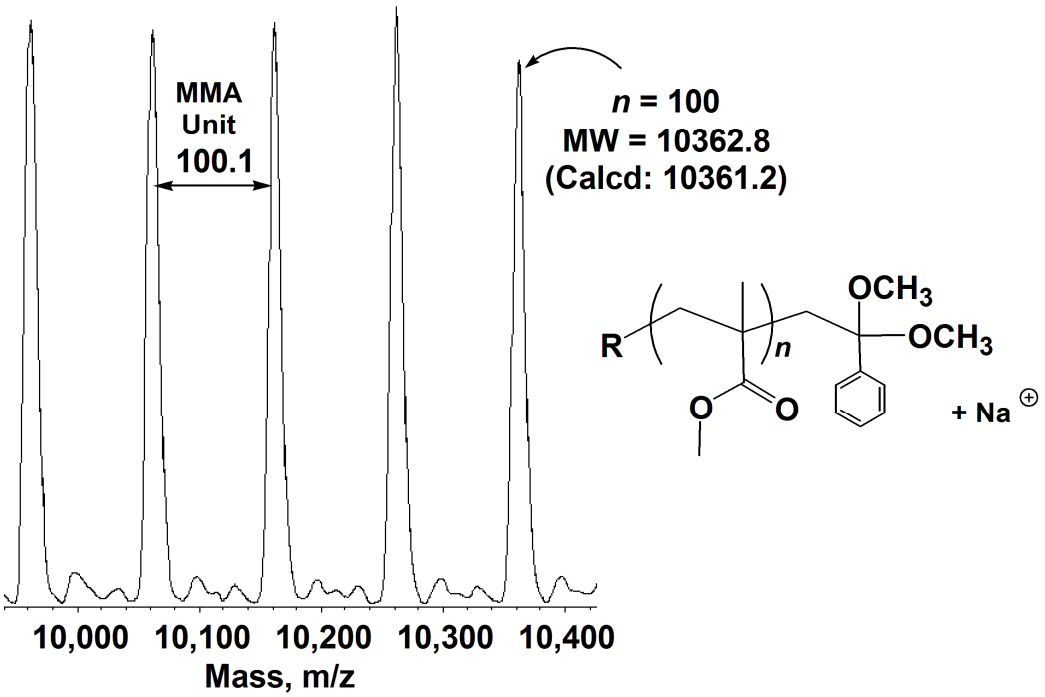


Figure 7. MALDI-TOF-MS spectrum of obtained PMMA in direct end-capping reaction with αMOS/methanol for ruthenium-catalyzed living radical polymerization of MMA. See Figure 6 for the conditions.

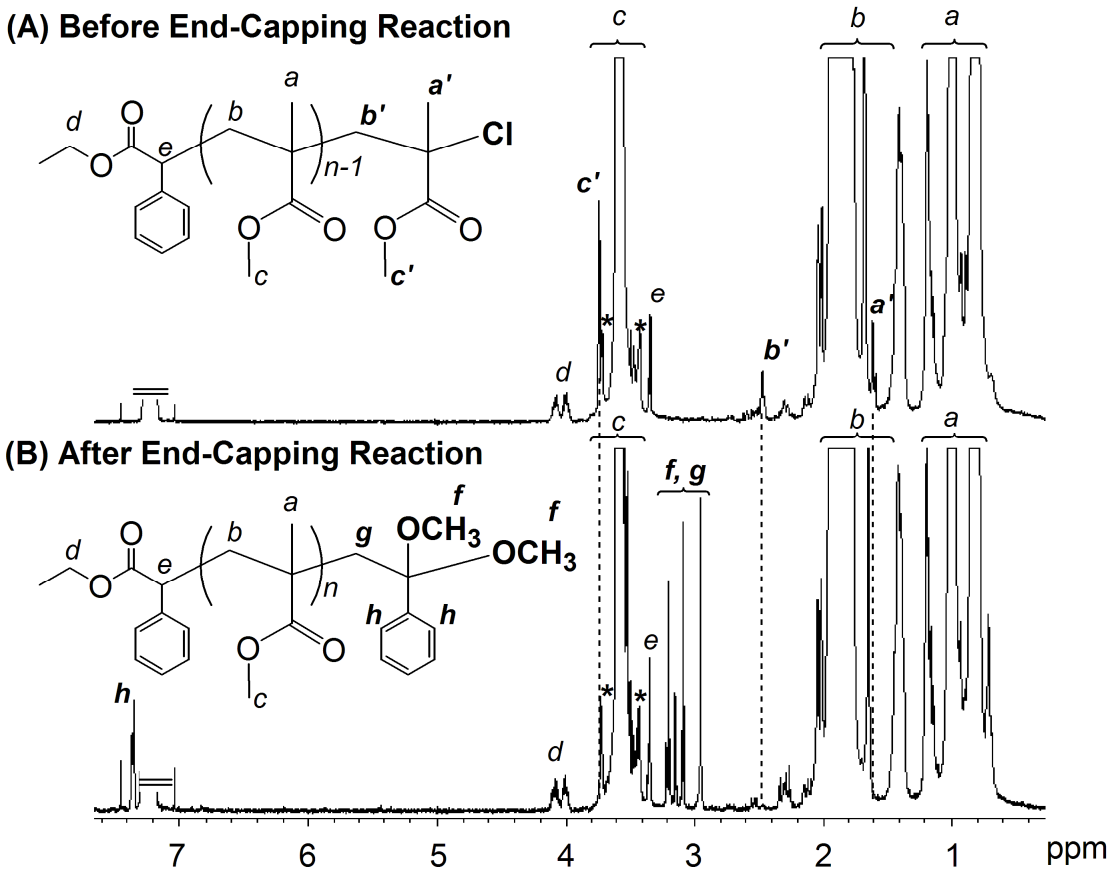


Figure 8. ^{1}H NMR analyses of obtained PMMAs in direct end-capping reaction with αMOS/methanol for ruthenium-catalyzed living radical polymerization of MMA. The asterisks (*) indicate satellite peaks. (A) Before the addition of αMOS/methanol. (B) After the addition. See Figure 6 for the conditions.

the expected PMMA with a single unit of αMOS and methoxy. The original NMR peaks from the Cl terminal disappeared: methyl (*a'*, 1.6 ppm), methylene (*b'*, 2.4 ppm) and methoxy (*c'*, 3.7 ppm)]; instead new peaks from the methoxy terminal appeared: methoxy and methylene (*f*, g 2.9-3.4 ppm) and aromatic (*h*, 7.4 ppm).

Thus, the direct end-capping at the later stage of polymerization was found to be effective, clean, and in particular simpler without an additional MMA removal. Note that this method cannot be available unless the polymerization is precisely controlled even at high monomer conversion.

5. Versatility: Scope of Monomers.

Finally, the alkoxy end-capping methodology was applied for monomers other than MMA, such as methyl acrylate (MA) and styrene (St). For these less reactive monomers, initiator/catalyst combinations were accordingly modified to be best fit for their respective

Table 1. Alkoxy End-Capping Reaction for Various Polymers with αMOS and MeOH[a]

Monomer	Initiator	Catalyst	Before Reaction		After Reaction		Alkoxy-End Functionality[b]
			M_n	M_w/M_n	M_n	M_w/M_n	
MMA	ECPA	$Ru(Ind)Cl(PPh_3)_2$	4,300	1.25	4,400	1.25	0.98
MA	H-EMA-Br	$Ru(Cp^*)Cl(PPh_3)_2$	4,900	1.18	4,900	1.18	0.92
St	H-EMA-Br	$Ru(Ind)Cl(PPh_3)_2$	5,200	1.20	5,300	1.20	0

[a] Polymerization: $[Monomer]_0$ = 2.0 M; $[Initiator]_0$ = 20 mM; $[Catalyst]_0$ = 2.0 mM; $[n\text{-}Bu_3N]_0$ = 20 mM in toluene at 80 ˚C for 13 h (MMA), at 80 ˚C for 15 h (MA), or at 100 ˚C for 24 h (St); End-capping reaction: $[\alpha MOS]_{add}$ = 200 mM; $[MeOH]_{add}$ = 2.0 M; $[n\text{-}Bu_3N]_{add}$ = 20 mM in toluene at 80 ˚C for 8 h. [b] Determined by ^1H NMR.

living radical polymerizations: H–EMA–Br/$Ru(Cp^*)Cl(PPh_3)_2$ for MA[17] and H–EMA–Br/ $Ru(Ind)Cl(PPh_3)_2$ for styrene.[10] As with MMA, when monomer conversion reached 40-50%, residual monomers were removed by evaporation before addition of αMOS and methanol. At this point the polymers from MA and styrene were well controlled and of narrow MWDs ($M_w/M_n \sim 1.2$).

Table 1 summarizes the structural characterizations of the resultant polymers after the umpolung and end-capping. For MA, the methoxy group was almost quantitatively introduced via one unit of αMOS without side reactions ($F_n \sim 0.92$ by ^1H NMR). For styrene, in contrast, no methoxy group was detected by NMR, indicating neither αMOS nor methanol reacted, probably because of the low reactivity of the styryl radical toward electron-rich αMOS.

Conclusion

The author demonstrated a novel method for a quantitative substitution of terminal-halogen in PMMA obtained with ruthenium-catalyzed living radical polymerization. The crucial point is a modification of the terminal carbon halogen bond to be polarized for an acceptance of ionic substitution by alcohol, which was brought about by attaching a modifier monomer with conjugated and electron-donating substituents, such as pMOS and αMOS. This method would be developed for various functionalizations at terminal with use of the corresponding alcohols.

Experimental Section

Materials

MMA (Tokyo Kasei; purity > 99%), methyl acrylate (MA, Tokyo Kasei; >99%) and styrene (St, Wako; >99%) were dried overnight over calcium chloride and distilled twice from calcium hydride under reduced pressure before use. Ethyl 2-chloro-2-phenylacetate (ECPA, Aldrich; >97%), ethyl 2-bromoisobutyrate (H-EMA-Br, Tokyo Kasei; >98%) were distilled under reduced pressure before use. 2,2-Dichloroacetophenone (Aldrich; 97%) was distilled from calcium hydride under reduced pressure before use. $Ru(Ind)Cl(PPh_3)_2$ (Strem) and $Ru(Cp^*)Cl(PPh_3)_2$ (Aldrich) were used as received and handled in a glove box under a moisture- and oxygen-free argon atmosphere (H_2O < 1 ppm, O_2 < 1 ppm). *n*-Octane (internal standard for gas chromatography for MMA) was dried overnight over calcium chloride and purified by double distillation from calcium hydride before use. Methanol (MeOH, Wako; dehydrated), 4-penten-1-ol (Aldrich; 99%), ethylene glycol (Aldrich; anhydrous, 99.8%) and *n*-Bu_3N (Tokyo Kasei; >99%) was bubbled with dry nitrogen for more than 15 min before use. Toluene (solvent) was passed through purification column (Solvent Dispensing System; Glass Contour) before use. *p*-Methoxystyrene (pMOS, Aldrich; >97%) and α-methylstyrene (αMeSt, Tokyo Kasei; >99%) were washed with 10% aqueous sodium hydroxide and then with saturated aqueous sodium chloride, dried overnight over sodium sulfate, and distilled under reduced pressure before use. α-Methoxystyrene (αMOS)[18] and α-methyl-*p*-methoxystyrene (αMepMOS)[19] were prepared according to the literature. Isobutyl vinyl ether (IBVE, Tokyo Kasei; > 99%) was washed with 10% aqueous sodium hydroxide and then with water, dried overnight over potassium hydroxide, and distilled twice from calcium hydride before use. 1,1-Diphenylethylene (DPE, Wako; >95%) was dried overnight over sodium sulfate and distilled under reduced pressure before use.

Polymerization and End-Capping Reaction

The polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock. A typical procedure is given below for an acetal-capped poly(MMA) (Scheme 2; R^1 = OMe; $R^2 = C_6H_5$), namely, the polymerization of MMA with ECPA/$Ru(Ind)Cl(PPh_3)_2$/*n*-Bu_3N and the subsequent sequential end-capping reaction with αMOS and then methanol: In an argon-filled glass tube was placed $Ru(Ind)Cl(PPh_3)_2$ (0.01 mmol, 7.76 mg), to which toluene (3.45 mL), *n*-octane (0.13 mL),

n-Bu_3N (0.25 mL, as a 400 mM solution in toluene, 0.1 mmol), MMA (1.07 mL, 10 mmol), and ECPA (0.10 mL, as a 995.8 mM solution in toluene, 0.1 mmol) were added sequentially in this order at room temperature under dry argon. The total volume of the reaction mixture was thus 5.0 mL. Immediately after mixing, the mixture was placed in an oil bath kept at 80 °C for 13 h. The polymerization solution was evaporated under an inert and air-free atmosphere to remove the residual monomer. Toluene (4.21 mL), *n*-Bu_3N (0.25 mL, as a 400 mM solution in toluene, 0.1 mmol), methanol (0.41 mL, 10 mmol), and αMOS (0.13 mL, 1.0 mmol) were added sequentially, and the mixture was placed again in an oil bath kept at 80 °C. In predetermined intervals, aliquots of the solution were sampled out and terminated by cooling to –78°C to monitor the progress of the reaction. Monomer conversion was determined from the concentration of residual monomer measured by gas chromatography with *n*-octane as an internal standard. The quenched reaction solutions were evaporated to dryness to give the products, which were subsequently vacuum-dried overnight.

Transformation of Acetal Terminal into Ketone

An acid solution, 1.0 M HCl aq. (0.07 mL), was added to a $CHCl_3$ solution of the acetal-capped polymer (0.03 g, 0.6 mL), and the mixture was stirred at room temperature for 24 h. The solution was evaporated to dryness to give the ketone-capped product, –MMA–$CH_2C(O)C_6H_5$.

Measurements

The M_n, M_w/M_n, and MWD curves of the polymers were determined by size-exclusion chromatography (SEC) in chloroform at 40 °C using three polystyrene gel columns [Shodex K-805L (pore size: 20-1,000 A; 8.0 mm i.d. × 30 cm) × 3; flow rate 1.0 mL/min] that were connected to a Jasco PU-980 precision pump, a Jasco RI-930 refractive index detector, and a Jasco UV/vis detector set at 250 nm. The columns were calibrated against 12 standard poly(MMA) samples (Polymer Laboratories; M_n = 630-1,200,000; M_w/M_n = 1.06-1.22). ^1H NMR spectra were recorded in $CDCl_3$ at room temperature on a JEOL JNM-LA500 spectrometer, operating at 500.16 MHz. Polymer samples for ^1H NMR were fractionated by preparative SEC (column: Shodex K-5002F). MALDI-TOF-MS analysis was performed on a Shimadzu AXIMA-CFR instrument equipped with 1.2 m linear flight tubes and a 337 nm nitrogen laser with dithranol (1,8,9-anthracenetriol) as an ionizing matrix and sodium trifluoroacetate as a cationizing agent.

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PART III

Control of Monomer Sequence

Chapter 5

In-Situ Monomer Transformation with Alcohols: Gradient Copolymers via Concurrent Tandem Living Radical Polymerization

Abstract

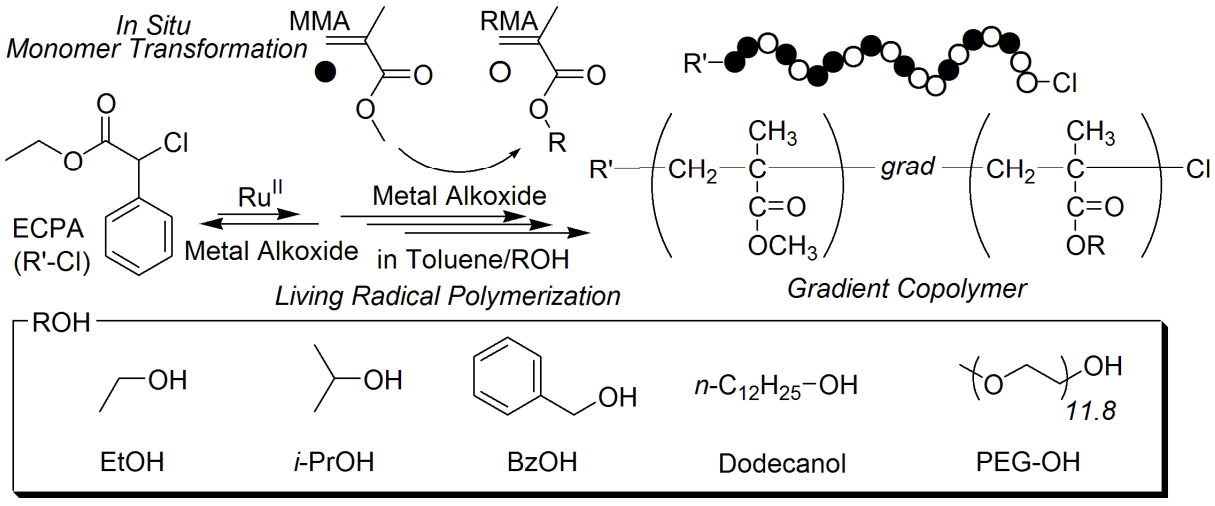
The author developed concurrent tandem living radical polymerization as a novel methodology to efficiently, conveniently, and in one-pot produce gradient copolymers via in-situ monomer transformation. The key is to employ a metal alkoxide [Al(O*i*-Pr)$_3$, Ti(O*i*-Pr)$_4$] and an alcohol solvent (ROH) in ruthenium-catalyzed polymerization of conventional ester-based methyl (meth)acrylate [M(M)A], where the monomer was in-situ transformed into R(M)A via in-situ transesterification to gradually vary the monomer composition during the copolymerization. Typically, MMA was polymerized with a ruthenium catalyst in the presence of excess ethanol (EtOH) and Al(O*i*-Pr)$_3$ cocatalyst to give well-controlled gradient copolymers from MMA to EMA along a polymer chain, in which the original MMA was gradually converted into ethyl methacrylate (EMA) by the cocatalyst. This concurrent tandem polymerization, in conjunction with a wide variety of alcohols, efficiently and conveniently produced various gradient copolymers including long alkyl chain and PEG pendent groups. The obtained copolymers further exhibited unique physical properties different from the corresponding random and block counterparts.

Introduction

An exquisite catalysis in polymer and materials chemistry implies an efficient, convenient, and versatile transformation from common reagents into functional designer materials. In terms of the efficiency and convenience, "tandem catalysis"[1] would be a candidate in which a simple one-pot synthetic approach involves multiple reactions concurrently or sequentially proceeding in a single raction vessel without isolation of intermediates. Such methodologies have been extended to certain precision polymer syntheses coupled with hydrogenation,[2] racemization,[3] side chain functionalization,[4] and different polymerization system.[5]

Transition metal-catalyzed living radical polymerization,[6] due to the high tolerance to polar functional groups including protic alcohols, now affords such functionalized polymers as end-functionalized,[7] star,[8] and gradient.[9] In these controlled radical processes, some additional cocatalysts[6,10] often play a vital role, in addition to initiators (organic halides) and metal complex catalysts. Among these cocatalysts are included metal alkoxides, which are quite effective not only in ruthenium-mediated system[10] but also in transesterification of esters with alcohols.[11]

Intrigued in this particular aspect of metal alkoxides, the author herein reports a concurrent tandem living radical polymerization via in-situ monomer transformation,[12] or a novel synthetic strategy for the synthesis of gradient copolymers (Scheme 1), whose efficiency, convenience, and versatility are clearly superior to those of the two conventional



Scheme 1. Concurrent Tandem Living Radical Polymerization for Gradient Copolymers via In-Situ Monomer Transformation of MMA

methods, one based on comonomer reactivity difference and the other on gradient feeding of comonomers.[9] The key is to employ a metal alkoxide [Al(O*i*-Pr)$_3$ or Ti(O*i*-Pr)$_4$][10] and an alcohol solvent (ROH) in the ruthenium-catalyzed living radical polymerization of unsaturated ester monomers such as methyl methacrylate (MMA) and methyl acrylate (MA). Combination of these metal alkoxides and alcohol solvents induces an in-situ transesterification of the pendent esters just in the monomers and not in the polymers, concurrently with propagation, and thereby allows gradual changes in feed monomer composition and, in turn, in copolymer composition along the main chain. Note that, for this to be achieved, the propagation should be living, or practically free from termination and chain transfer.

Results and Discussion

1. Gradient Copolymers via In Situ Transesterification.

First, transesterification of MMA was examined with Al(O*i*-Pr)$_3$ or Ti(O*i*-Pr)$_4$ in ethanol (EtOH)/toluene (1/1, v/v) at 80 °C (Figure 1A). Both metal alkoxides efficiently catalyzed the reaction to give ethyl methacrylate (EMA) in high yield (>80%), where the activity of Al(O*i*-Pr)$_3$ was lower than that of Ti(O*i*-Pr)$_4$ [50 h, conv. 75% (Al), 95% (Ti)].

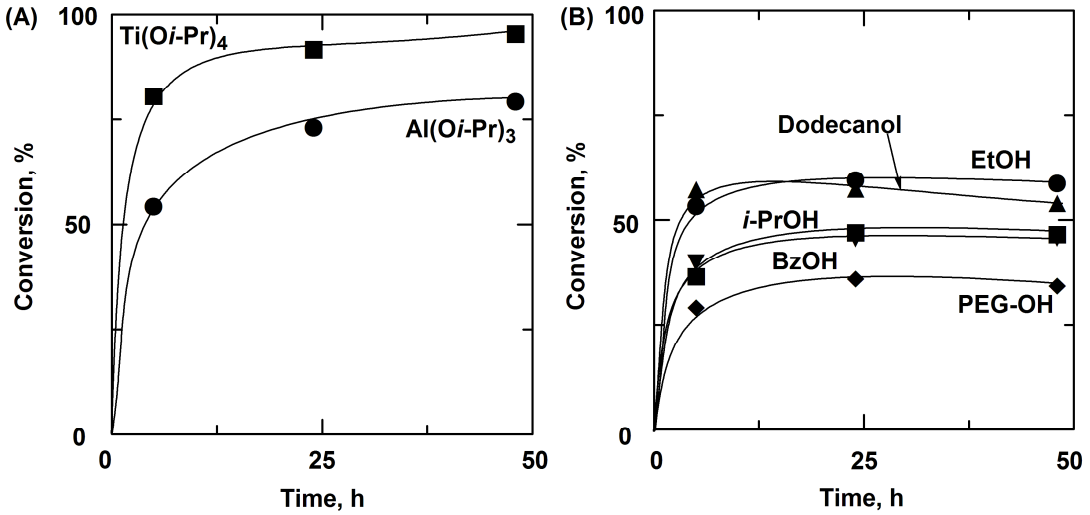


Figure 1. Metal alkoxide-catalyzed transesterification of MMA with alcohols. (A) Effects of metal alkoxide: $[MMA]_0$ = 2.0 M; $[\text{metal alkoxide}]_0$ = 20 mM in toluene/EtOH (1/1, v/v) at 80 ˚C. (B) Effects of alcohols: $[MMA]_0$ = 2.0 M; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM; $[\text{alcohol}]_0$ = 2.0 M or 1.5 M (PEG-OH) in toluene at 80 ˚C.

To well synchronize the gradual compositional change in monomer and their copolymerization, Al(O*i*-Pr)$_3$ was employed as a cocatalyst for MMA; catalyst, Ru(Ind)Cl(PPh$_3$)$_2$, Ind = η^5- C$_9$H$_7$]; initiator, ethyl 2-chloro-2-phenylacetate (ECPA); solvent, EtOH/toluene (1/1, v/v) at 80 °C. The polymerization smoothly proceeded to a high total monomer conversion, and the molecular weight distribution (MWD) of the obtained polymers, as measured by SEC, was narrow and shifted to higher molecular weight as the conversion increased (48 h: 93%, M_n = 11,300, M_w/M_n = 1.32) (Figure 2A, 2B). Direct ^{1}H NMR analysis of the polymerization mixtures actually revealed the gradual increase of EMA contents (Figure 2A, dash lines and 2C).

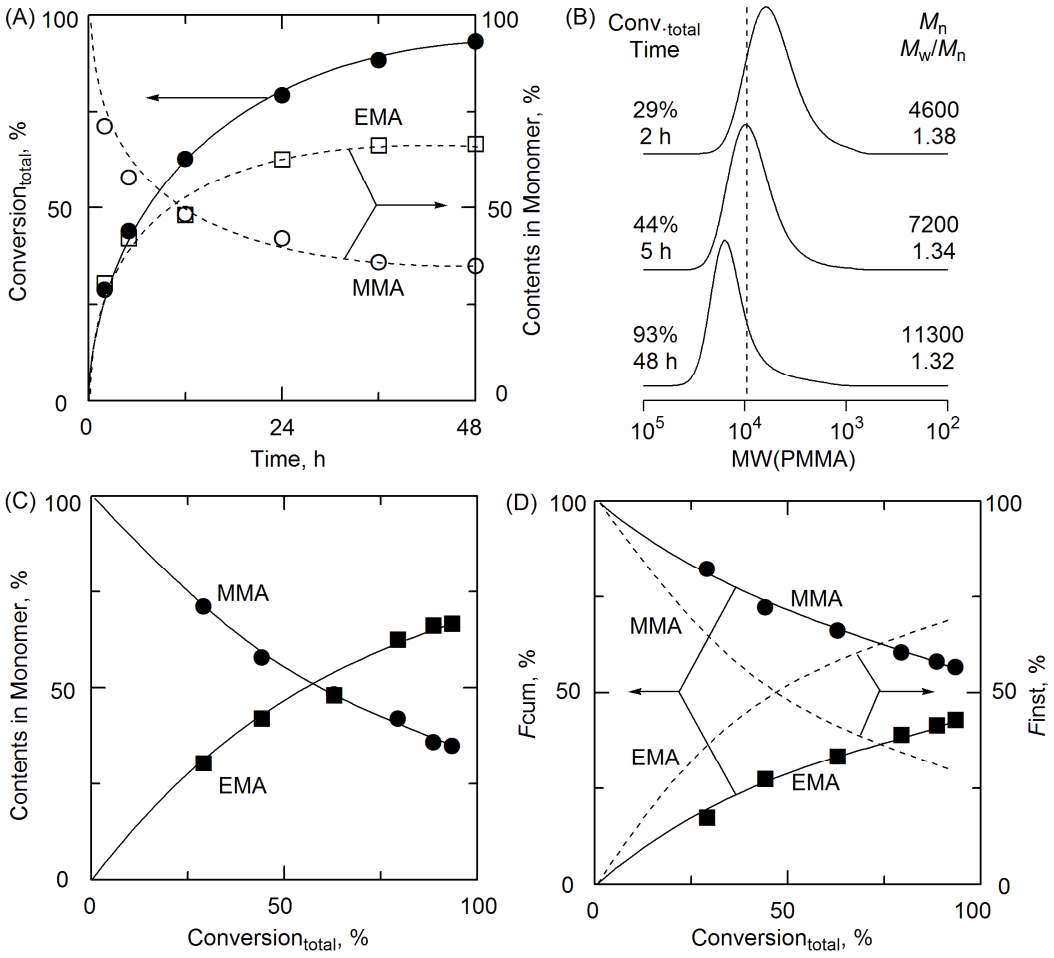


Figure 2. Concurrent tandem living radical copolymerization of MMA via in-situ transesterification: (A) total conversion and monomer contents of MMA and EMA in polymerization solution, and (B) SEC curves of products during the polymerization; (C) monomer contents in polymerization solution, and (D) cumulative (F_{cum}) or instantaneous (F_{inst}) monomer contents in products as a function of total conversion; [MMA]$_0$ = 2.0 M; [ECPA]$_0$ = 20 mM; [Ru(Ind)Cl(PPh$_3$)$_2$]$_0$ = 2.0 mM; [Al(O*i*-Pr)$_3$]$_0$ = 20 mM in toluene/EtOH (1/1, v/v: [EtOH]$_0$ = 6.5 M) at 80 °C.

The cumulative EMA content ($F_{cum,\ EMA}$), obtained by ^{1}H NMR for each conversion, gradually increased from 0 to ca. 45%, while that of MMA ($F_{cum,\ MMA}$) in turn decreased (Figure 2D, solid line). The instantaneous EMA content ($F_{inst,\ EMA}$: Figure 2D, dash line), calculated from the differential increase in $F_{cum,\ EMA}$, also gradually increased with the total conversion from 0 to 68%, suggesting that gradient copolymers were obtained via a concurrent tandem living radical polymerization.[9]

2. Mechanism.

In the absence of Al(O*i*-Pr)$_3$, no pendent transesterification proceeded, and the polymerization was also retarded in the latter stage where the originally brown solution turned dark brown indicating some catalyst deactivation (Figure 3). These indicate a dual role of Al(O*i*-Pr)$_3$ as a catalyst in transesterification and a cocatalyst in polymerization. More importantly, the pendent group transformation proceeded specifically on MMA monomer and not on its polymers, as indicated by a separate observation that a poly(MMA) sample

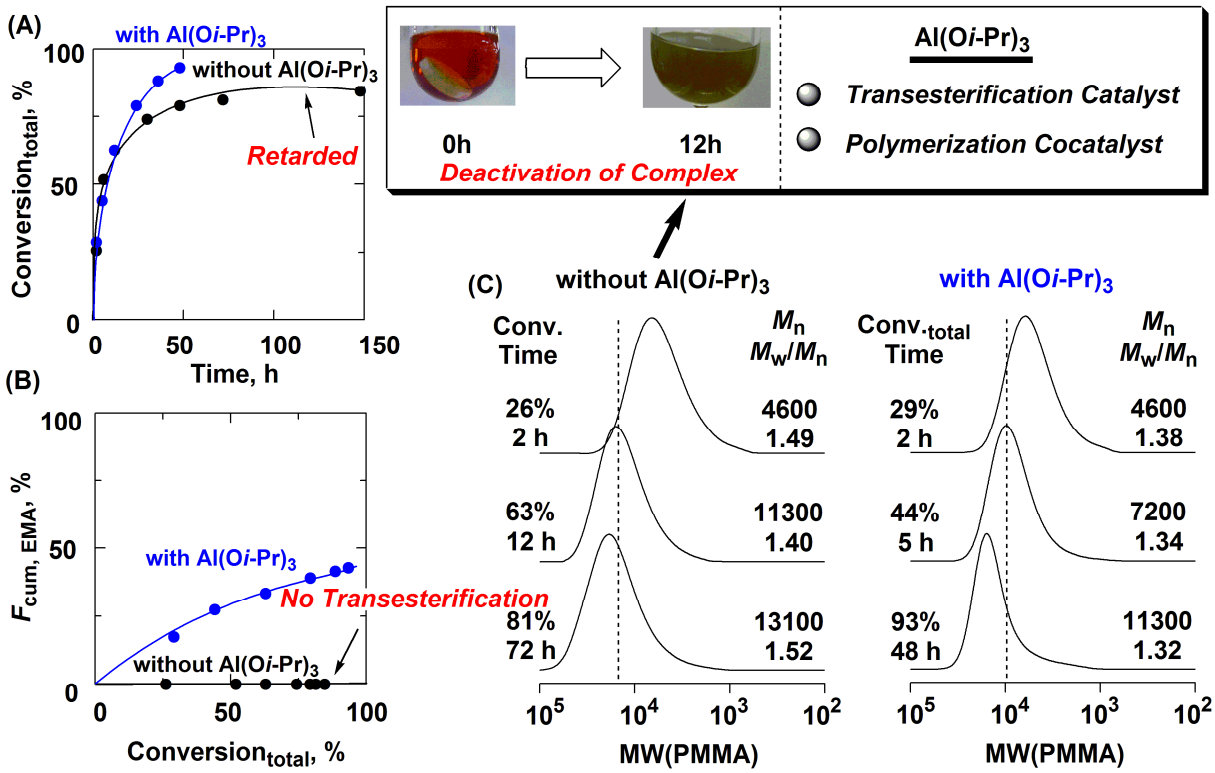


Figure 3. Living radical polymerization of MMA in the absence or presence of Al(O*i*-Pr)$_3$: (A) total conversion as a function of polymerization time, (B) cumulated EMA contents ($F_{cum,\ EMA}$) in polymers as a function of total conversion, (C) MWD curves of obtained polymers with or without Al(O*i*-Pr)$_3$; $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(Oi\text{-}Pr)_3]_0$ = 0, 20 mM in toluene/EtOH (1/1, v/v) at 80 ˚C.

(M_n = 12,500, M_w/M_n = 1.14) was not transesterified with Al(O*i*-Pr)$_3$ in EtOH under similar conditions (Figure 4). In addition, the ruthenium-catalyzed random copolymerization of MMA and EMA gives almost the same monomer reactivity ratios (Figure 5). Thus, the instantaneous composition (MMA/EMA ratio) in products (F_{inst}) is in fact determined only by the corresponding in-situ monomer composition (Figure 2C and 2D, dash lines).

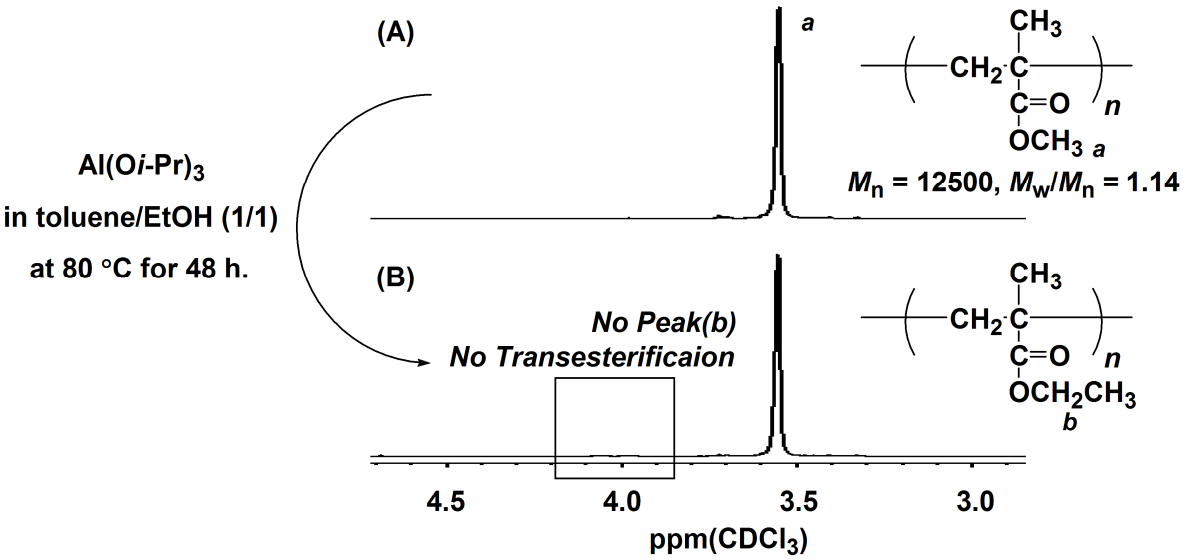


Figure 4. ^{1}H NMR spectra of PMMA (A) before and (B) after the treatment of transesterification condition with Al(O*i*-Pr)$_3$ in toluene/EtOH (1/1, v/v) at 80 ˚C: $[PMMA]_0$ = 20 mM; $[Al(Oi\text{-}Pr)_3]_0$ = 20 mM. PMMA was obtained from ECPA/Ru(Ind)Cl(PPh$_3$)$_2$/*n*-Bu$_3$N in toluene at 80 ˚C: M_n = 12500, M_w/M_n = 1.14.

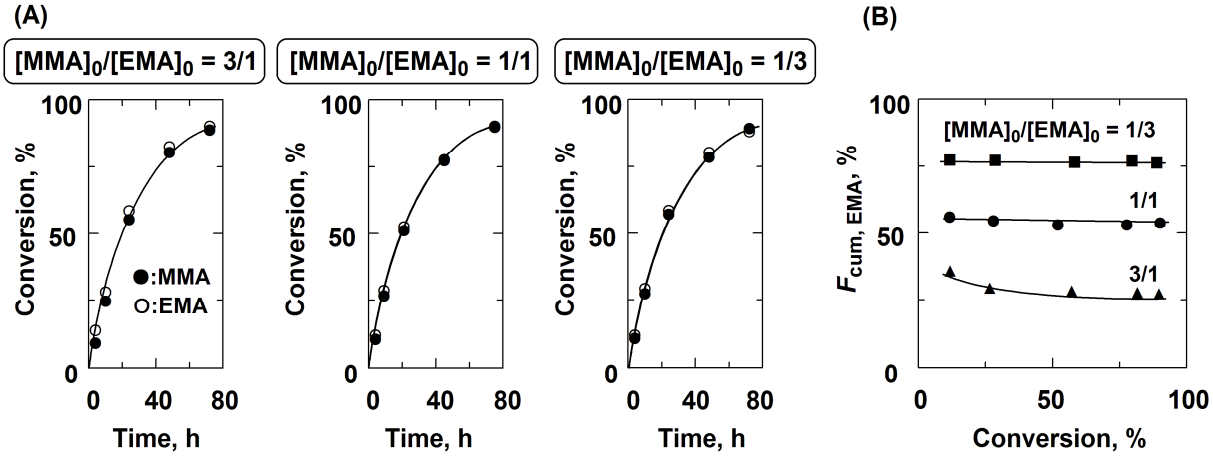
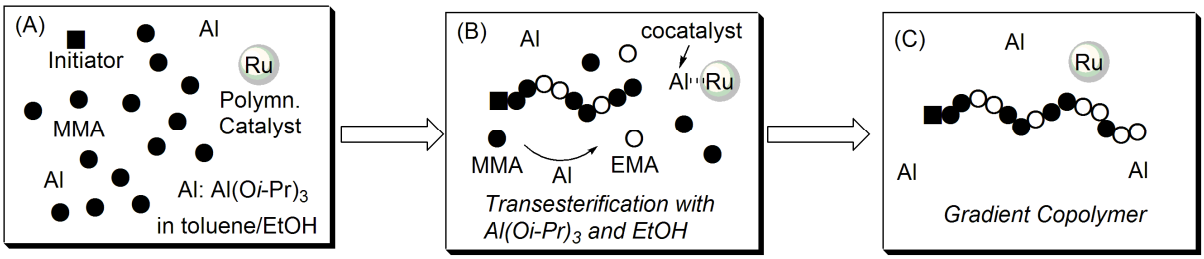


Figure 5. Ruthenium-catalyzed living radical random copolymerization of MMA and EMA with ECPA/Ru(Ind)Cl(PPh$_3$)$_2$/Al(O*i*-Pr)$_3$: (A) monomer conversion as a function of polymerization time and (B) cumulated EMA contents ($F_{cum, EMA}$) in polymers as a function of monomer conversion; $[MMA]_0 + [EMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(Oi\text{-}Pr)_3]_0$ = 20 mM in toluene at 80 ˚C.

Therefore, these results strongly support the proposed tandem catalysis (Scheme 2), where Al(O*i*-Pr)$_3$-catalyzed selective transesterification of MMA with EtOH gradually produces EMA during the polymerization and thereby continuously vary the monomer composition in the solution (A to B), finally giving well-controlled gradient copolymers of MMA and EMA (C). In addition, Al(O*i*-Pr)$_3$, after treatment with EtOH, completely turned into Al(OEt)$_3$, which would be a true cocatalyst in this tandem copolymerization.



Scheme 2. Proposed Mechanism of Concurrent Tandem Living Radical Polymerization for Gradient Copolymers via In-Situ Transesterification of MMA

3. Versatility.

The author then applied various alcohols such as isopropanol (secondary), benzyl alcohol, dodecanol (long alkyl), and poly(ethylene glycol) (PEG) methyl ether (polymeric), to the tandem copolymerization of MMA (Table 1, entry 2–5). Ti(O*i*-Pr)$_4$[10] was employed as a

Table 1. Various Gradient Copolymers via Concurrent Tandem Polymerization[a]

entry	alcohol	time (h)	M_n[b]	M_w/M_n[b]	$F_{cum,\,M(M)A}/F_{cum,\,R(M)A}$[c]
1	EtOH	36	11,200	1.36	28/72
2	*i*-PrOH	33	11,900	1.37	55/45
3	BzOH	22	11,900	1.45	55/45
4	Dodecanol	22	20,700	1.21	56/44
5[d]	PEG-OH	10	28,000	1.17	69/31
6[e]	EtOH	72	7,700	1.66	45/55

[a] $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM in toluene/alcohol (1/1) at 80 ˚C; Conv. > 80 %. [b] Measured by SEC. [c] Calculated from ^{1}H NMR. [d] $[MMA]_0$ = 0.5 M; $[ECPA]_0$ = 5.0 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM in PEG-OH. [e] $[MA]_0$ = 2.0 M; [Ethyl 2-bromoisobutyrate]$_0$ = 20 mM; $[Ru(Cp^*)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(O\textit{i}\text{-}Pr)_3]_0$ = 20 mM; $[n\text{-}Bu_3N]_0$ = 20 mM. Cp*: η^5-$C_5(CH_3)_5$

metal alkoxide to realize transesterification with various alcohols (Figure 1B). All these reactions efficiently produced well-controlled gradient copolymers derived from the corresponding alcohols (Figure 6). This system can be further extended to methyl acrylate (MA) (entry 6), giving acrylic gradient copolymers.

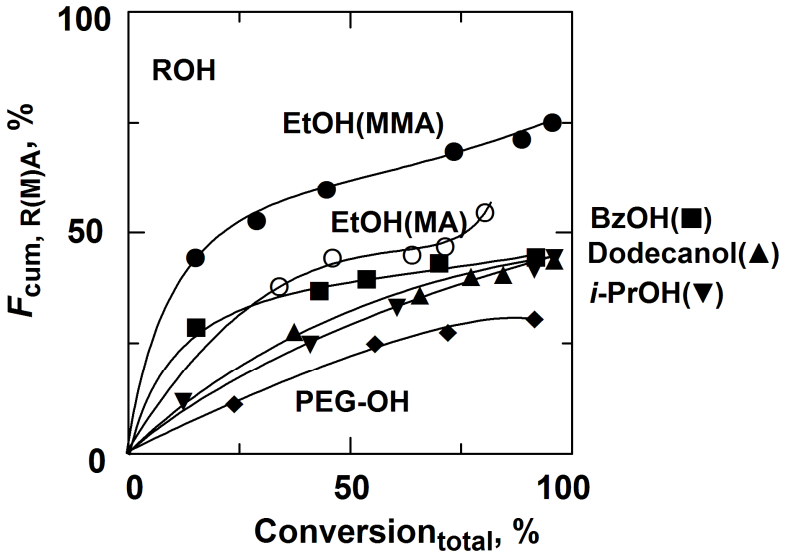


Figure 6. Cumulated R(M)A contents ($F_{cum,\ R(M)A}$) in polymers obtained from ruthenium-catalyzed concurrent tandem living radical polymerization of M(M)A in the presence of various alcohols and Ti(O*i*-Pr)$_4$, as a function of total monomer conversion. See Table 1 for the reaction conditions.

4. Physical Properties.

The gradient copolymers showed unique physical properties, differentiating them from the corresponding random and block counterparts. For example, the copolymers with 1-dodecanol exhibited a broad glass transition temperature (by differential scanning calorimetry) (Figure 7).[13] Additionally, the solubility of the PEG-bearing gradient copolymers in 2-propanol (3 wt%) was thermosensitive with an upper critical solution temperature (UCST: ca. 19 °C) clearly lower than for the corresponding random copolymers (ca. 37 °C) (Figure 8).[8b]

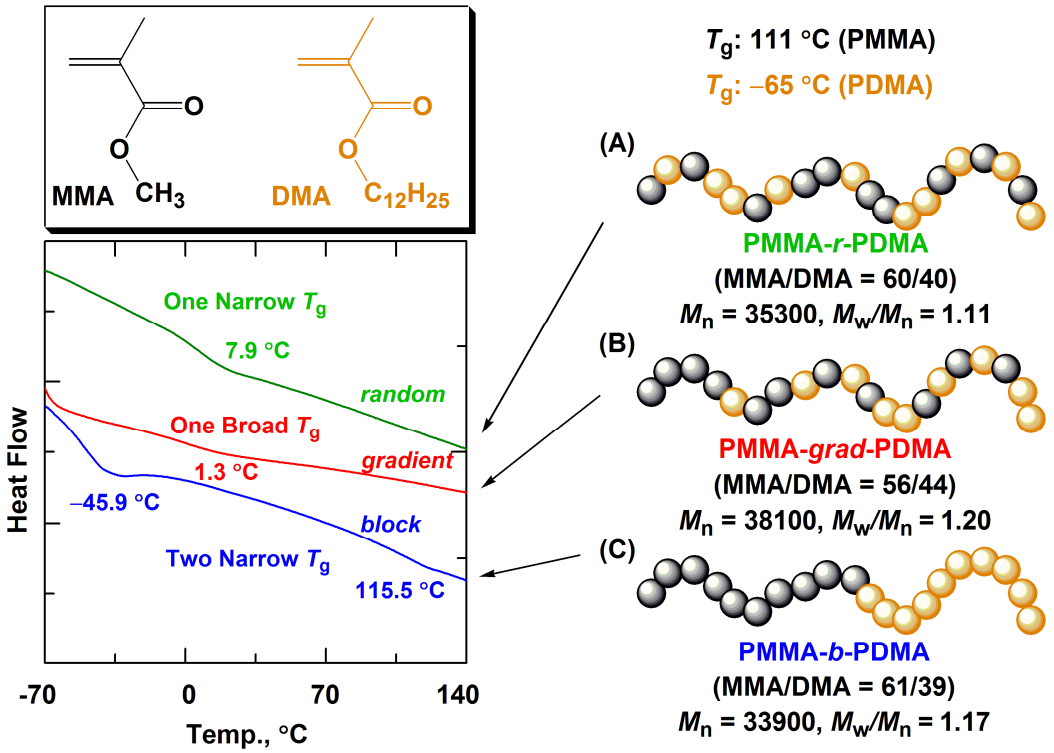


Figure 7. DSC curves of copolymers of MMA and dodecyl methacrylate (DMA) obtained from ruthenium-catalyzed living radical polymerization. (A) Random: $[MMA]_0$ = 1.0 M; $[DMA]_0$ = 1.0 M; $[ECPA]_0$ = 5.0 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM in toluene at 80 ˚C. (B) Gradient: $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 5.0 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM in toluene/1-dodecanol (1/1, v/v) at 80 ˚C. (C) Block: $[PMMA\text{-}Cl]_0$ = 10 mM; $[DMA]_0$ = 2.0 M; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM in toluene at 80 ˚C. PMMA-Cl: ω-end chlorine-capped poly(MMA) obtained with ECPA/$Ru(Ind)Cl(PPh_3)_2$/*n*-Bu_3N in toluene at 80 ˚C; M_n = 12500, M_w/M_n = 1.14.

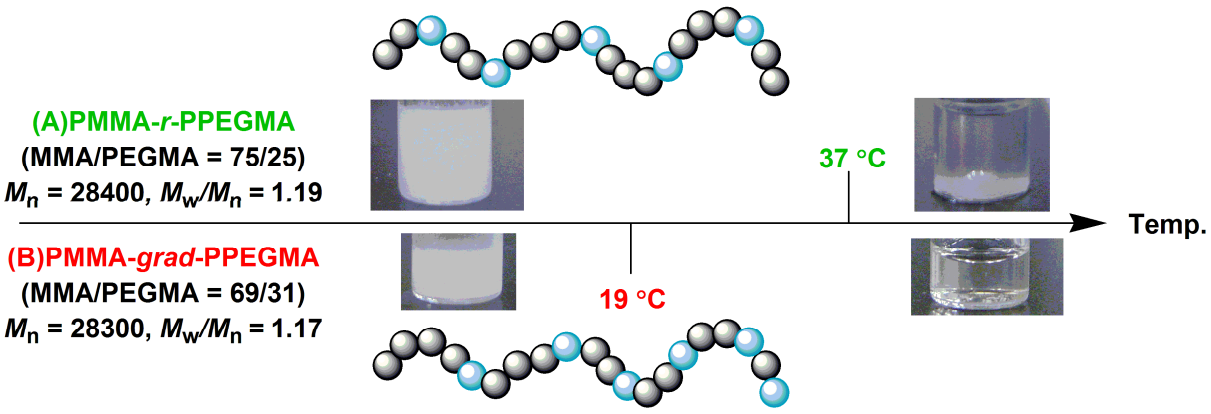


Figure 8. Photographs of methacrylate-based copolymers with random or gradient poly(ethylene glycol) (PEG) pendant in 3 wt% 2-propanol solution for upper critical solution temperature (UCST). (A) Random: $[MMA]_0$ = 2.0 M; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM; $[ECPA]_{add}$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_{add}$ = 2.0 mM in PEG-OH at 80 ˚C. (B) Gradient: $[MMA]_0$ = 0.5 M; $[ECPA]_0$ = 5.0 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM in PEG-OH at 80 ˚C.

Conclusion

The author developed a novel concurrent tandem living radical polymerization, where metal-catalyzed copolymerization and metal alkoxide-catalyzed transesterification of a simple methyl (meth)acrylate with various alcohols were synchronized with propagation to produce controlled gradient copolymers, efficiently, conveniently, and in one pot. This methodology opened up new vistas to produce well-defined materials from simple and common alcohols.

Experimental Section

Materials

MMA (Tokyo Kasei, purity > 99%) and MA (Tokyo Kasei, >99%) were dried overnight over calcium chloride and distilled twice from calcium hydride under reduced pressure before use. Ethyl 2-chloro-2-phenylacetate (ECPA, Aldrich, >97%) and ethyl 2-bromoisobutyrate (Tokyo Kasei, >98%) were distilled under reduced pressure before use. $Ru(Ind)Cl(PPh_3)_2$ (Aldrich), $Ru(Cp^*)Cl(PPh_3)_2$ (Aldrich), $Al(O\textit{i}\text{-}Pr)_3$ (Aldrich, >99%), and $Ti(O\textit{i}\text{-}Pr)_4$ (Kanto Chemicals, >97%) were used as received and handled in a glove box under moisture- and oxygen-free argon (H_2O < 1 ppm; O_2 < 1 ppm). Ethanol (EtOH) (Wako, dehydrated), 2-propanol (*i*-PrOH) (Wako, dehydrated), benzyl alcohol (BzOH) (Wako, >99%), 1-dodecanol (Dodecanol) (Wako, >95%), poly(ethylene glycol) methyl ether (PEG-OH) (Aldrich: M_n = 550), and $n\text{-}Bu_3N$ (Tokyo Kasei, >99 %) were degassed before use. Tetralin (1,2,3,4-tetrahydronaphthalene) (Kishida Chemical, >98%) as internal standard for ^1H NMR analysis was dried overnight over calcium chloride and purified by double distillation from calcium hydride before use. Toluene (solvent) was purified before use by passing through a purification column (Solvent Dispensing System; glass contour).

Tandem Polymerization

The polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock. Typical procedures for tandem polymerization of MMA with ECPA/$Ru(Ind)Cl(PPh_3)_2$/$Al(O\textit{i}\text{-}Pr)_3$ in toluene/EtOH (1/1, v/v): Into a glass tube with $Ru(Ind)Cl(PPh_3)_2$ (4.46 mg , 0.006 mmol) were added toluene (0.56 mL), tetralin (0.08 mL), $Al(O\textit{i}\text{-}Pr)_3$ (0.48 mL of 125 mM in toluene, 0.06 mmol), MMA (0.64

mL, 6 mmol), EtOH (1.14 mL), and ECPA (0.1 mL of 610.0 mM in toluene, 0.06 mmol), sequentially in this order, at room temperature under dry argon. The total volume of the reaction mixture was thus 3.0 mL. The glass tube was immediately placed in an oil bath kept at 80 °C. The reaction was followed by taking aliquots of the solution with a syringe under dry argon in predetermined intervals and then terminating by cooling to –78 °C. Total monomer conversion and the monomer composition in a polymerization solution, and the repeat-unit composition of polymers were determined by ^{1}H NMR in $CDCl_3$ with tetralin as an internal standard. The quenched reaction solutions were washed with water and evaporated to dryness to give the products, which were subsequently vacuum-dried overnight.

Measurements

The M_n, M_w/M_n, and MWD curves of the polymers were determined by size-exclusion chromatography (SEC) in chloroform at 40 °C using three polystyrene gel columns [Shodex K-805L (pore size: 20-1000 A; 8.0 mm i.d. × 30 cm) × 3; flow rate 1.0 mL/min] that were connected to a Jasco PU-980 precision pump, a Jasco RI-930 refractive index detector, and a Jasco UV/vis detector set at 250 nm. The columns were calibrated against 10 standard poly(MMA) samples (Polymer Laboratories; M_n = 630–1,200,000; M_w/M_n = 1.06–1.22). ^{1}H NMR spectra were recorded in $CDCl_3$ at room temperature on a JEOL JNM-LA500 spectrometer operating at 500.16 MHz. Differential scanning calorimetry was performed on polymer samples (ca. 4 mg weighed into an aluminum pan) under a dry nitrogen flow at a heating or cooling rate of 20 °C/min on a DSCQ200 calorimeter (TA Instruments) equipped with a RCS 90 electric freezing machine. Polymer samples for ^{1}H NMR and DSC analysis were fractionated beforehand by preparative SEC (column: Shodex K-5002 F).

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Chapter 6

Sequence-Regulated Copolymers: Tandem Catalysis of Living Radical Polymerization and Transesterification with Alcohols

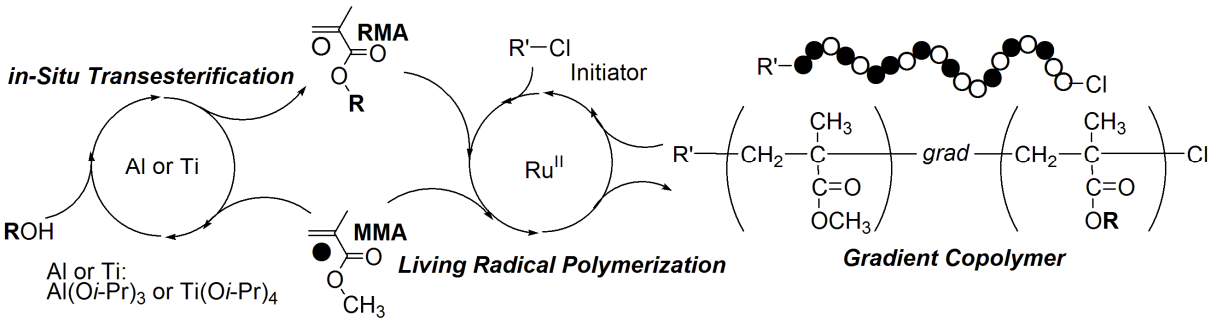
Abstract

Monomer sequence regulation along a single polymer chain is undoubtedly still remaining and challenging issue as an ultimate goal in the field of polymer science. In this work, sequence-controlled copolymers were successfully synthesized, in one-pot, by efficient, convenient, and versatile tandem catalysis combined with metal alkoxide/alcohol-mediated transesterification of methacrylates and ruthenium-catalyzed living radical polymerization of their monomers. The concurrent tandem catalysis induced in-situ transformation of a monomer into another monomer as well as their polymerization to efficiently produce various gradient copolymers. The key is the transesterification highly selective for monomers and not for the dimmer and the oligo(poly)mers. The monomer sequence in the obtained gradient copolymer was controlled by species and/or concentrations of metal alkoxides and alcohols, and the reaction temperature. Monomer-selective or iterative transesterification gave random-gradient copolymers or gradient-block counterparts, respectively. Additionally, this tandem catalysis can be applied to not only the synthesis of gradient copolymers but also that of random or block copolymers by controlling the initiation of transesterification and polymerization. This tandem catalytic system should open new ways to prepare sequence-regulated copolymers.

Introduction

Natural polymers such as proteins, enzymes, and genes, own perfectly controlled primary structures. The sequence regulation of the main chain is a key player to create their exquisite functions like efficient and selective catalysis, and transmission of genetic information. In synthetic polymers, recent development of precision polymerization, typically represented by living radical polymerization,[1-7] has allowed us to control most of primary structures including molecular weight, molecular weight distribution, terminal structure, and three-dimensional architectures. Monomer sequence regulation along a single polymer chain[8] is, however, still remaining and challenging issue as an ultimate goal for synthetic polymers via precision polymerization. So far, except for conventional random, alternating, and gradient copolymerization, some new approaches were examined to achieve the sequence regulation. The typical representatives are the followings: 1) iterative in-situ addition of functional monomers into polymerization;[9] 2) polymerization of monomers comprising a designer sequence;[10,11] 3) radical addition with template-bearing initiators with specific interaction to monomers.[12] Though these methodologies are efficient, they often include multi-step procedures or bothersome syntheses.

Ideal catalysis and synthetic method for functional designer materials should be efficient, convenient, and versatile transformation with common reagents. In terms of the efficiency and convenience, tandem catalysis is the typical representative to realize multiple reactions in one-pot sequentially and/or concurrently proceeding in a single reaction vessel without any isolation of intermediates. Such strategies have actually applied to several precision polymerization in conjunction with hydrogenation,[13,14] racemization,[15] click reaction,[16] and different polymerization system.[17,18] Thanks to the high tolerance to functional groups, transition metal-catalyzed living radical polymerization is also versatile enough to design functional polymers.[1-4] For example, ruthenium catalysts achieved the synthesis of well-defined functional (co)polymers in alcohols,[19] even in the presence of water,[20] without any retardation. In these systems, cocatalysts are often employed to improve the controllability of the polymerization.[21,22] Metal alkoxides such as Al(O*i*-Pr)$_3$ and Ti(O*i*-Pr)$_4$ are one of the effective cocatalysts (additives) in ruthenium-catalyzed polymerization,[22] while they are also catalysts suitable for transesterification of ester compounds in the presence of alcohols.[23]



Scheme 1. Tandem Catalysis of Living Radical Polymerization and Transesterification for Gradient Copolymers

Focusing on the intriguing dual roles of metal alkoxides, the author has quite recently developed concurrent tandem living radical polymerization as a novel methodology to produce gradient copolymers[24] via in-situ monomer transformation, efficiently, conveniently, and in one-pot (Scheme 1).[25] The key is to employ a metal alkoxide and an alcohol solvent (ROH) in ruthenium-catalyzed living radical polymerization of conventional ester-based methyl methacrylate (MMA). Importantly, in-situ transesterification proceeded for pendent esters just in monomers and not in the polymers to give RMA and the monomer composition gradually varied during the copolymerization.

Herein, the author reports the synthesis of sequence-regulated copolymers via tandem catalysis consisting of metal alkoxides-mediated transesterification of methacrylates in the presence of alcohols and ruthenium-catalyzed living radical polymerization of their comonomers. Discussion was especially directed to the catalytic sequence regulation of gradient copolymers via the species of metal alkoxides (cocatalyst) and monomers, concentration of the cocatalysts and alcohols, and reaction temperature. This tandem catalysis further applied to various sequence-regulated copolymers including block, random, gradient-block, and random-gradient copolymers (Figure 1).

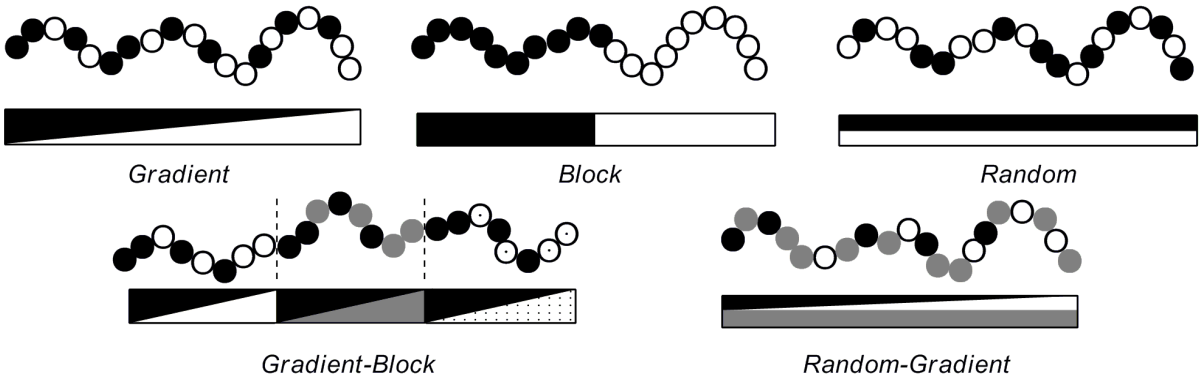


Figure 1. Sequence-controlled copolymers via tandem catalysis

Results and Discussion

1. Transesterification for Tandem Catalysis.

Concurrent tandem transesterification suitable for ester pendant-bearing gradient copolymers in ruthenium-catalyzed living radical polymerization needs to satisfy the three following factors:[25] (i) transesterification selectively occurring in monomer and not in the polymer, or in monomer much prior to the polymers; (ii) cooperative catalysis and kinetics with ruthenium-mediated polymerization; (iii) no deactivation of polymerization system (catalysts, halogen terminal) by the catalysts for transesterification. Thus, the author systematically investigated metal-catalyzed transesterification of (meth)acrylates in the presence of alcohols suitable for the concurrent tandem catalysis.

Al(O*i*-Pr)$_3$ or Ti(O*i*-Pr)$_4$ were employed for transesterification of MMA, MA and their polymers in EtOH/toluene (1/1, v/v) at 80 °C (Figure 2). The metal alkoxides are typical cocatalysts for ruthenium-catalyzed living radical polymerization, thus never deactivate the polymerization.[22] Both metal alkoxides showed the high reaction selectivity for MMA into ethyl methacrylate (EMA) and not for PMMA (M_n = 12500) (Figure 2A), and Ti(O*i*-Pr)$_4$ was more active than Al(O*i*-Pr)$_3$.[25] The author further examined effects of the degree of polymerization (*DP*) of methyl methacrylate in Al(O*i*-Pr)$_3$-catalyzed transesterification. Importantly, though MMA and its saturated ester, methyl isobutyrate, were smoothly transformed into the corresponding ethyl esters, even a model compound of a MMA dimer, 2-chloro-2,4,4-tri-methylglutarate, hardly reacted, and MMA poly(oligo)mers over 14 of *DP* were completely inert (Figure 2B). This is probably because the aluminum catalysts are

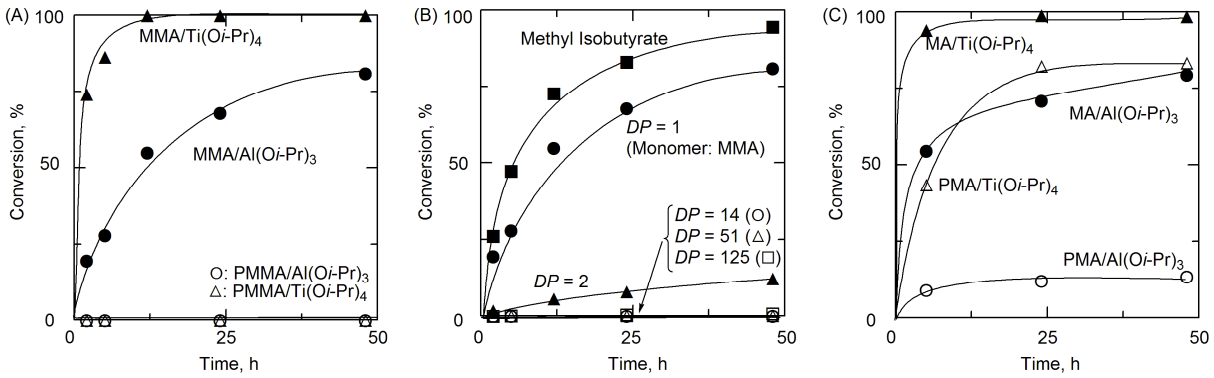


Figure 2. Metal alkoxide-catalyzed transesterification of MMA and MA in toluene/EtOH (1/1, v/v) at 80 ˚C. (A) [MMA]$_0$ or [PMMA (M_n = 12500)]$_0$ = 20 mM; [Al(O*i*-Pr)$_3$]$_0$ or [Ti(O*i*-Pr)$_4$]$_0$ = 20 mM. (B) [MMA]$_0$ or [PMMA]$_0$ = 20 mM; [Al(O*i*-Pr)$_3$]$_0$ = 20 mM. (C) [MA]$_0$ or [PMA (M_n = 8000)]$_0$ = 20 mM; [Al(O*i*-Pr)$_3$]$_0$ or [Ti(O*i*-Pr)$_4$]$_0$ = 20 mM.

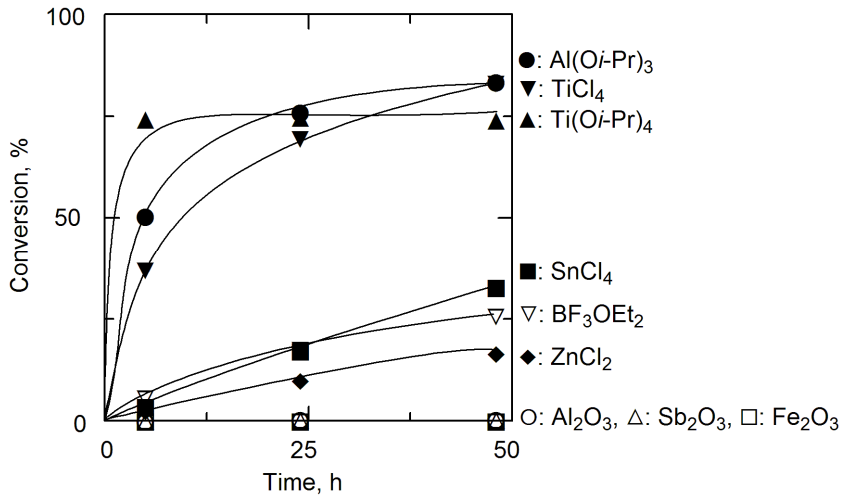


Figure 3. Effects of Lewis acid in transesterification of MMA with EtOH: $[MMA]_0$ = 2.0 M; $[Lewis\ acid]_0$ = 100 mM in toluene/EtOH (1/1, v/v) at 80 °C.

sterically and structurally hindered from accessing to the pendant esters in the oligomers and/or polymers by the methacrylate backbones and lots of the neighboring pendants. The high selectivity is a crucial factor to synthesize gradient copolymers via concurrent tandem catalysis with in-situ transesterification of monomers. In contrast, MA polymers were more reactive than MMA counterparts in the similar transesterification, probably due to the flexible backbone derived from acrylates (Figure 2C).[26] Other metal compounds such as titanium(IV), tin(IV), and zinc chlorides ($TiCl_4$, $SnCl_4$, $ZnCl_2$), boron trifluoride diethyl etherate (BF_3OEt), and aluminum, antimony(III), iron(III) oxides (Al_2O_3, Sb_2O_3, Fe_2O_3) were also examined for the transesterification of MMA (Figure 3). However, the metal halides were clearly less effective than the metal alkoxides [Al(O*i*-Pr)$_3$ and Ti(O*i*-Pr)$_4$], and the metal oxides never induced the reaction. Thus, it revealed that the aluminum and titanium alkoxides were most suitable as catalysts for in-situ transesterification of MMA.

2. Concurrent Tandem Living Radical Polymerization.

Catalytic Sequence Control: Gradient Copolymers. Monomer-sequence control in gradient copolymers was examined by concurrent tandem catalysis of metal alkoxide-catalyzed transesterification of MMA into EMA in the presence of EtOH and ruthenium-catalyzed living radical polymerization of the resulting comonomers. Discussion was directed to the effects of catalyst species, reaction temperature, and the concentrations of Al(O*i*-Pr)$_3$ and EtOH, in comparison to the independent experiments of the corresponding transesterification.

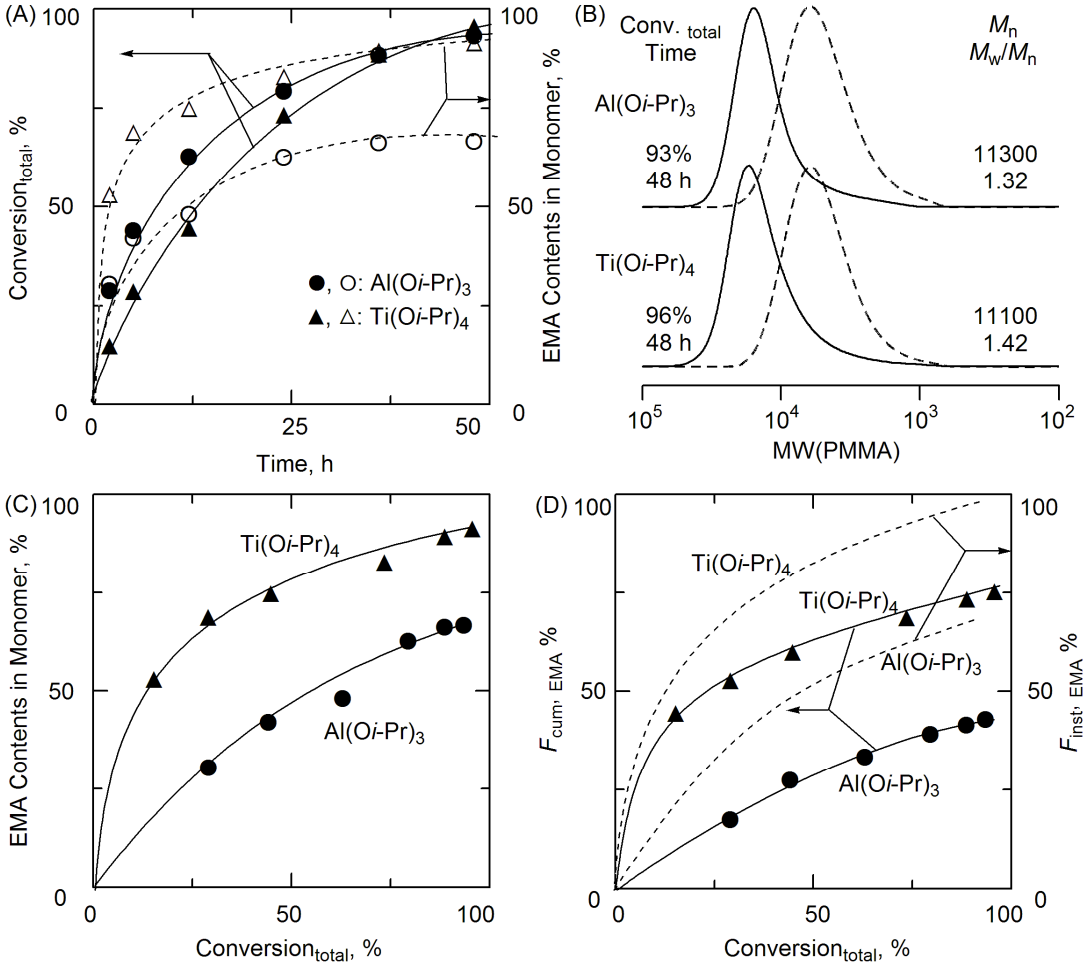


Figure 4. Effects of metal alkoxides in concurrent tandem living radical polymerization: (A) total conversion and EMA contents in polymerization solution; (B) SEC curves of products during the polymerization; (C) EMA contents in polymerization solution; (D) cumulative ($F_{cum, EMA}$) or instantaneous ($F_{inst, EMA}$) EMA contents in products as a function of total conversion: $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[metal\ alkoxide]_0$ = 20 mM in toluene/EtOH (1/1, v/v) at 80 °C.

To investigate effects of metal alkoxides on a monomer sequence in gradient copolymers, the author first compared Al(O*i*-Pr)$_3$ and Ti(O*i*-Pr)$_4$ as cocatalysts in MMA polymerization coupled with a ruthenium catalyst [Ru(Ind)Cl(PPh$_3$)$_2$, Ind = η^5-C$_9$H$_7$],[27] and ethyl 2-chloro-2-phenylacetate (ECPA: initiator)[28] in EtOH/toluene mixture (1/1, v/v) at 80 °C (Figure 4). Both polymerizations smoothly proceeded up to over 90% total conversion. Ethyl methacrylate (EMA) simultaneously and gradually formed in the both solutions (Figure 4A). The resulting copolymers had well-controlled molecular weights and narrow molecular weight distributions (MWDs) (Figure 4B). Incorporation of EMA units into all polymer chain was confirmed by MALDI-TOF-MS (Figure 5). The cumulative EMA contents

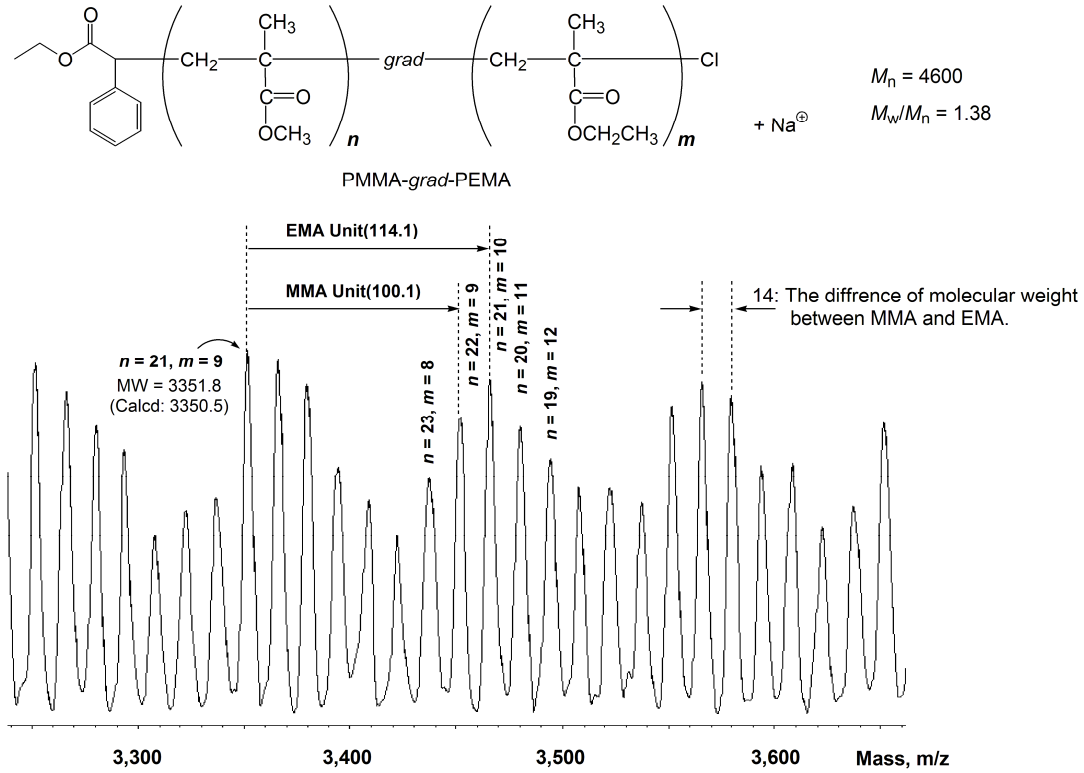


Figure 5. MALDI-TOF-MS spectrum of PMMA-*grad*-PEMA obtained from the tandem catalysis of living radical polymerization and transesterification of MMA in the presence of EtOH and Al(O*i*-Pr)$_3$: $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(O\textit{i}\text{-}Pr)_3]_0$ = 20 mM in toluene/EtOH (1/1, v/v) at 80 °C.

($F_{cum,\ EMA}$) and the instantaneous EMA contents ($F_{inst,\ EMA}$) in the both products, determined by ^{1}H NMR, gradually increased with increasing total monomer conversion (Figure 4D). The products thus consisted of gradient copolymers carrying MMA-rich segment around the α-end and EMA-rich one around the ω-end along with a single chain. $F_{inst,\ EMA}$ in the each system was fully consistent with the EMA monomer contents in each solution (Figure 4C, 4D).[25] As well as the independent transesterification of MMA (Figure 2A), Ti(O*i*-Pr)$_4$ induced in-situ transesterification of MMA to EMA in higher yield than Al(O*i*-Pr)$_3$, to give final gradient copolymers with higher EMA contents. More importantly, Al(O*i*-Pr)$_3$ induced catalysis synchronizing transesterification with polymerization in the initial stage, resulting in gradient copolymers whose EMA contents gradually increased from the α-end along a single chain. On the contrary, Ti(O*i*-Pr)$_4$ gave gradient copolymers including high EMA contents even around the α-end due to in-situ transesterification of MMA into EMA faster than ruthenium-catalyzed polymerization of their resulting monomers. Therefore, this tandem catalysis can catalytically control the monomer sequence in gradient copolymers on demands via metal alkoxide species.

Next, the author examined reaction temperature (40, 60, 80 °C), the concentrations of Al(O*i*-Pr)$_3$ (10, 20, 40 mM) and EtOH (1, 4, 6.5 M) in tandem catalysis of Al(O*i*-Pr)$_3$/EtOH-mediated transesterification of MMA into EMA and ruthenium-catalyzed copolymerization of their monomers. Figure 6 shows the cumulative EMA content ($F_{cum, EMA}$) in the products as a function of total monomer conversion. In all cases, polymerization

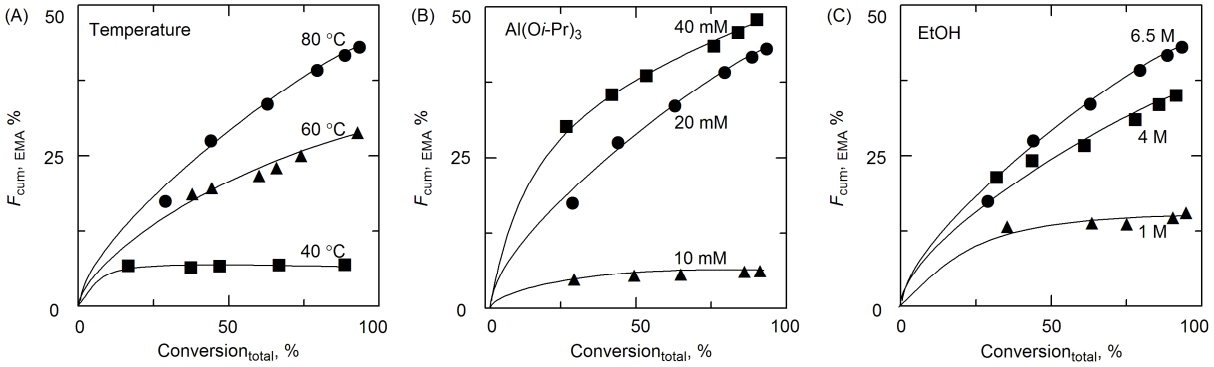


Figure 6. Control of the cumulative EMA contents ($F_{cum, EMA}$) by polymerization conditions in concurrent tandem polymerization: (A) $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(Oi\text{-}Pr)_3]_0$ = 20 mM in toluene/EtOH (1/1, v/v) at 40, 60, 80 °C. (B) $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(Oi\text{-}Pr)_3]_0$ = 10, 20, 40 mM in toluene/EtOH (1/1, v/v) at 80 °C. (C) $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(Oi\text{-}Pr)_3]_0$ = 20 mM; $[EtOH]_0$ = 1.0, 4.0, 6.5 M in toluene at 80 °C.

Table 1. Control of Monomer Sequence in Gradient Copolymers via Concurrent Tandem Catalysis[a]

Entry	$[Al(Oi\text{-}Pr)_3]_0$ (mM)	$[EtOH]_0$ (M)	Temp. (°C)	Time (h)	$Conv_{total}$ (%)[b]	M_n[c]	M_w/M_n[c]	$F_{cum, MMA}/F_{cum, EMA}$ (%/%)[b]
1	20	6.5	80	48	93	11,300	1.32	57/43
2	20	6.5	40	214	89	10,300	1.38	94/6
3	20	6.5	60	134	93	11,600	1.27	71/29
4	10	6.5	80	34	91	11,400	1.43	94/6
5	40	6.5	80	49	90	11,300	1.43	52/48
6	20	1.0	80	34	95	11,400	1.27	84/16
7	20	4.0	80	48	92	11,700	1.34	65/35

[a] $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM $[Al(Oi\text{-}Pr)_3]_0$ = 10 - 40 mM; $[EtOH]_0$ = 1.0 - 6.5 M in toluene at 40 - 80 °C. [b] Determined by ^{1}H NMR. [c] Measured by SEC.

smoothly proceeded up to about 90% conversion to give EMA-containing copolymers with well-controlled molecular weights and narrow MWD (Table 1), where the in-situ transesterification of MMA into EMA efficiently led to gradient copolymers form MMA to EMA, except for the polymerization at 40 °C and that with 10 mM Al(O*i*-Pr)$_3$. These tendencies were consistent with the identical transesterification of MMA with similar conditions. More importantly, $F_{cum,\ EMA}$ was higher with increasing the temperature and the concentrations of Al(O*i*-Pr)$_3$ and EtOH. Therefore, it revealed that the monomer sequence and the total monomer composition in gradient copolymers were also controlled by the reaction temperature and the concentrations of Al(O*i*-Pr)$_3$ and EtOH.

Selective Transesterification: Random-Gradient Copolymers. Bulkiness of an ester substitution strongly affects the reactivity of transesterification of ester compounds.[29] Focusing on the steric hindrance in pendant esters of methacrylates, various monomers such as *i*-PrMA (secondary) and *t*-BuMA (tertiary) were examined in comparison to MMA (primary) in ruthenium-catalyzed polymerization of MMA in conjunction with Ti(O*i*-Pr)$_4$ and EtOH at 80 °C (Figure 7). All of the polymerization smoothly proceeded to high conversion. However, it turned out that the in-situ transesterification occurs selectively for primary and secondary alkyl methacrylates and not for the tertiary analogue. Thus, the tandem polymerization of MMA or *i*-PrMA gave the respective gradient copolymers including EMA, whereas that of *t*-BuMA did a homopolymer, P*t*-BuMA. Based on this trick, MMA and *t*-BuMA were copolymerized with a ruthenium catalyst in the presence of Al(O*i*-Pr)$_3$ and

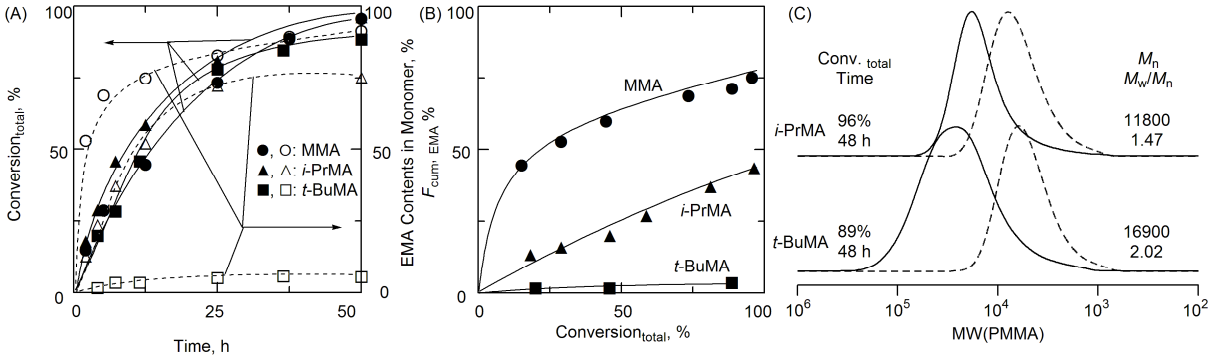


Figure 7. Concurrent tandem living radical copolymerization of various monomer: (A) total conversion and EMA contents in polymerization solution, (B) cumulative monomer contents in products (F_{cum}) as a function of total conversion, and (C) SEC curves of products with *i*-PrMA and *t*-BuMA, (see Figure 4 for that with MMA). [monomer]$_0$ = 2.0 M; [ECPA]$_0$ = 20 mM; [Ru(Ind)Cl(PPh$_3$)$_2$]$_0$ = 2.0 mM; [Ti(O*i*-Pr)$_4$]$_0$ = 20 mM in toluene/EtOH (1/1, v/v) at 80 °C.

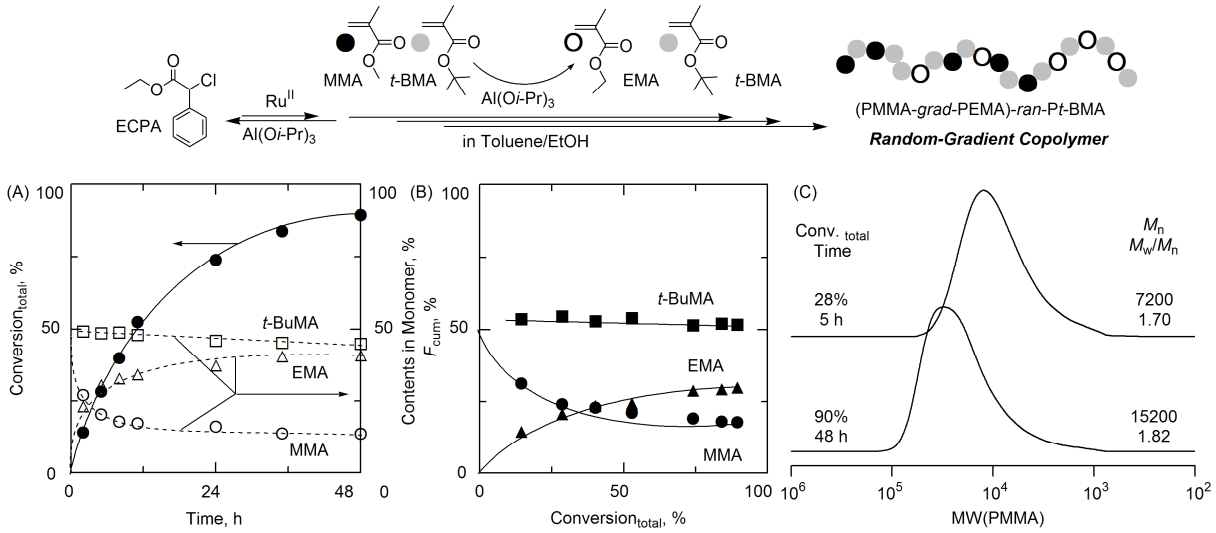


Figure 8. Random-gradient copolymers via concurrent tandem living radical copolymerization: (A) total conversion and monomer contents in polymerization solution, (B) cumulative monomer contents in products (F_{cum}) as a function of total conversion, and (C) SEC curves of products; $[MMA]_0$ = 1.0 M; $[t\text{-BuMA}]_0$ = 1.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(O\textit{i}\text{-}Pr)_3]_0$ = 20 mM in toluene/EtOH (1/1, v/v) at 80 °C.

EtOH (Figure 8). In fact, MMA was gradually and selectively tranformed into EMA along with polymerization except for *t*-BuMA, successfully leading to random-gradient copolymers.

3. Sequence and Segment-Controlled Copolymers.

Iterative Tandem Catalysis: Gradient-Block Copolymers. Thanks to the high catalyst stability and end-functionality, ruthenium-mediated polymerization realized one-pot block copolymerization with in-situ addition of a second monomer into a prepolymer solution.[1-4] Thus, the tandem catalysis was extended to the synthesis of gradient triblock copolymers containing three different gradient segments by the iterative addition of monomers and alcohols (Figure 9). In the presence of Ti(O*i*-Pr)$_4$, well-controlled PMMA-*grad*-P*i*-PrMA (1st block) was efficiently obtained from ruthenium-catalyzed polymerization of MMA with a chloride initiator (ECPA) in *i*-PrOH and toluene (1/1, v/v) at 80 ^{o}C. Then, the remaining monomers and solvents were removed by evaporation, followed by the addition of a fresh MMA, EtOH and toluene into the reaction vessel. The tandem polymerization sequentially restarted for 2nd block segment. Once again, an identical procedure with MMA and BzOH was conducted for 3rd block. The SEC curves of the products exhibited unimodal distributions and shifted to higher molecular weight distribution (Figure 9A). RMA, the methacrylate transesterified with the corresponding alcohol, contents in each segments ($F_{cum,}$

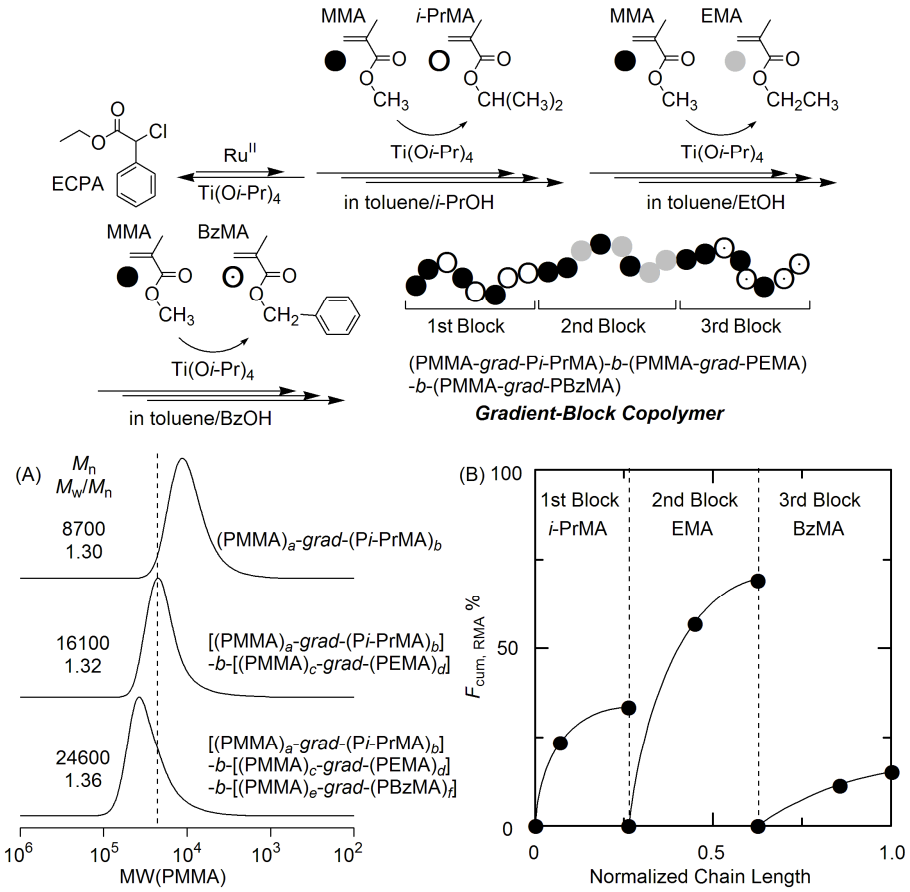


Figure 9. Gradient-block copolymer via iterative tandem polymerization. (A) SEC curves of products and (B) cumulative monomer contents in products ($F_{cum,\ RMA}$) as a function of the normalized chain length: $[MMA]_0$ = 2.0 M; $[ECPA]_0$ or $[macroinitiator]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM in toluene/alcohol (1/1, v/v) at 80 °C; a/b = 27/14, c/d = 18/39, e/f = 50/9. RMA is the monomer transesterified with the corresponding alcohol.

$_{RMA}$) efficiently increased in each segments as the copolymerization proceeded (Figure 9B), demonstrating that the iterative tandem catalysis led to gradient triblock copolymers. These results also strongly support that in-situ alkoxide-catalyzed transesterification never interferes in controllability and end-functionality of ruthenium-catalyzed living radical polymerization.

Sequential Initiation of Tandem Catalysis: Random or Block Copolymers. Concurrent tandem catalysis of polymerization and transesterification yields gradient copolymers due to their synchronizing catalysis. On the contrary, sequential initiation of polymerization or transesterification can also achieve the sequence control of copolymers, providing random or block copolymers, respectively (Figure 10). Typically, in-situ addition of an initiator and a ruthenium catalyst at the time transesterification of MMA into EMA reached the equilibrium

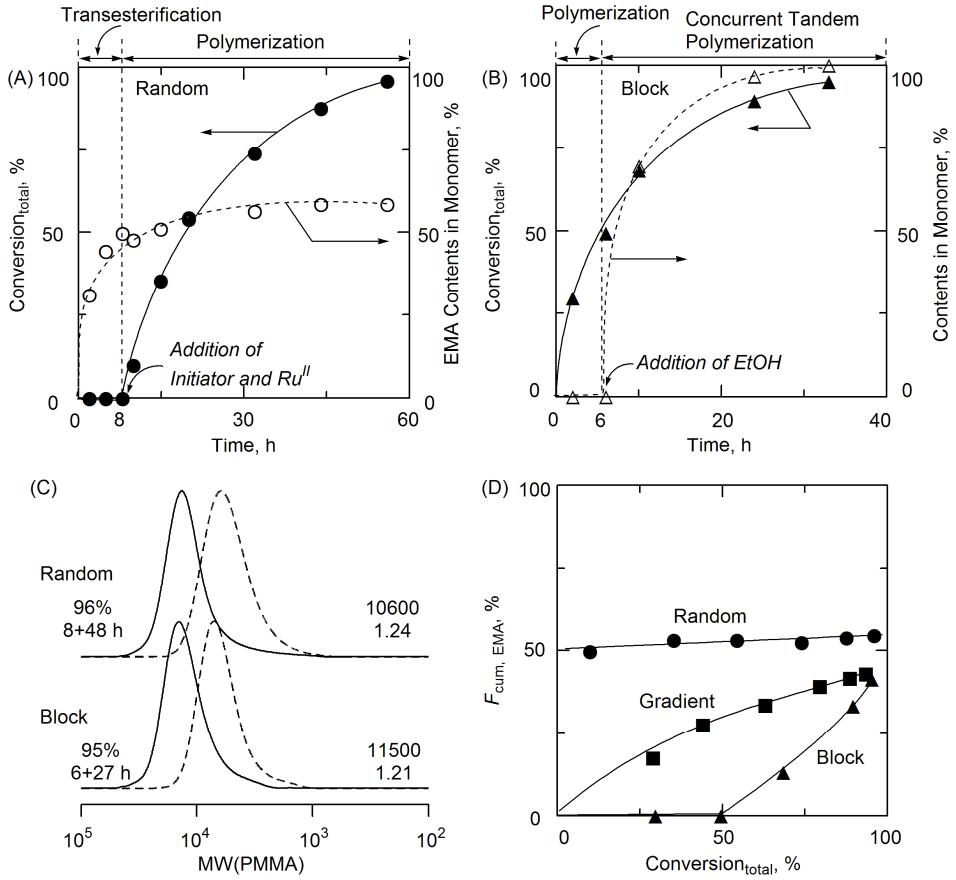


Figure 10. Effects of initiation timing of transesterification and polymerization in tandem living radical polymerization: (A), (B) total conversion and EMA contents in polymerization solution, (C) SEC curves of products, (D) cumulative EMA contents in products ($F_{cum,\ EMA}$) as a function of total conversion. Gradient: the same samples as the product with Al(O*i*-Pr)$_3$ in Figure 4. Random: $[MMA]_0$ = 2.0 M; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM; $[EtOH]_0$ = 2.0 M; $[ECPA]_{add}$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_{add}$ = 2.0 mM in toluene at 80 °C. Block: $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Ti(O\textit{i}\text{-}Pr)_4]_0$ = 20 mM; $[EtOH]_{add}$ = 6.5 M in toluene at 80 °C.

state (EMA contents: 50 - 55%) gave well-controlled random copolymers carrying homogeneous composition of EMA along a chain (Figure 10A). The constant $F_{cum,\ EMA}$ was fully consistent with the constant EMA contents during polymerization. On the other hand, in-situ addition of EtOH coupled with Ti(O*i*-Pr)$_4$ in the middle of MMA polymerization (MMA conversion ~ 50%) produced block-like copolymers consisting of a MMA homo-segment and a EMA-rich segment, since the titanium alkoxide-catalyzed transesterification of the remaining MMA into EMA was much faster than their copolymerization over 50% conversion of MMA (Figure 10B). These results also support that concurrent tandem catalysis of transesterification and copolymerization provides gradient copolymers in contrast to the sequential initiation of polymerization or transesterification.

4. Thermal Analysis.

The thermal property of gradient copolymers obtained form the concurrent tandem catalysis with MMA and various alcohols was investigated with differential scanning calorimetry (DSC) (Table 2). All samples showed one broad glass transition temperature (T_g) between T_g of MMA homopolymers and that of the RMA homopolymers, also strongly supporting the formation of gradient copolymer via tandem copolymerization.[30] T_g of MMA/EMA gradient copolymers decreased with increasing EMA contents (Entry 1-4), corresponding to the T_g of a EMA homopolymer (~ 57 °C)[31] lower than that of a MMA counterpart. T_g of methacrylate-based gradient copolymers with similar MMA contents (~55%) was also dependent on gradient monomer species originating from alcohols and monomers in tandem catalysis (Entry 3, 5-7). PEG-bearing gradient copolymers owned melting temperature (T_m) derived from PEG chains, in addition to the inherent T_g (Entry 8). These results show that the tandem catalysis can produce various materials with a broad range of thermal property.

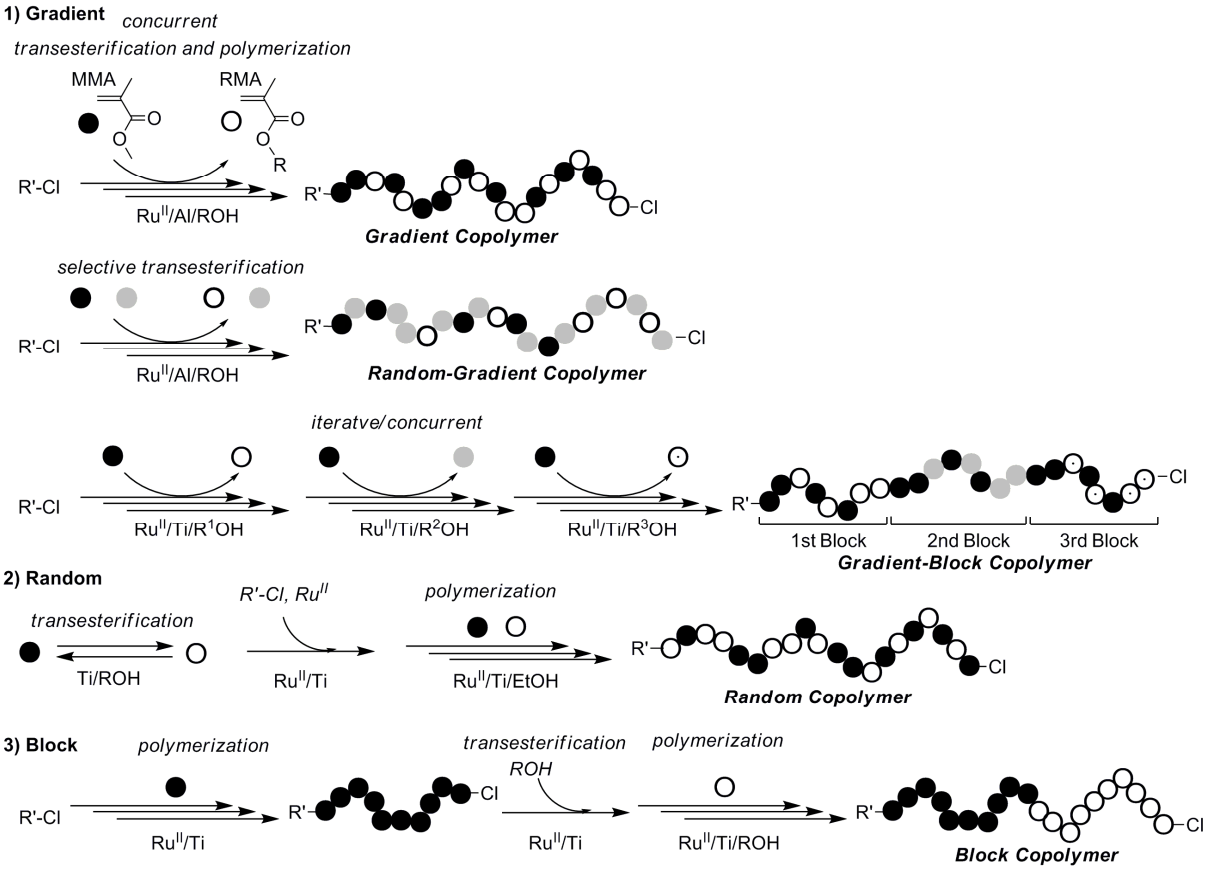
Table 2. Thermal Analysis of Various Gradient Copolymers via Concurrent Tandem Living Radical Polymerization[a]

Entry	Alcohols	M_n[b]	M_w/M_n[b]	$F_{cum,\,MMA}/F_{cum,\,RMA}$ (%)[c,d]	T_g [T_m] (°C)[e]
1[f]	EtOH	10,300	1.28	94/6	105
2[g]	EtOH	11,200	1.27	71/29	91
3	EtOH	11,300	1.32	57/43	88
4	EtOH	11,100	1.42	25/75	64
5	*i*-PrOH	11,900	1.37	55/45	81
6	BzOH	12,900	1.45	55/45	59
7	Dodecanol	20,700	1.21	56/44	18
8[h]	PEG-OH	28,000	1.17	69/31	-59 [11]

[a] $[MMA]_0$ = 2.0 M; $[ECPA]_0$ = 20 mM; $[Ru(Ind)Cl(PPh_3)_2]_0$ = 2.0 mM; $[Al(O\textit{i}\text{-}Pr)_3]_0$ (Entry 1-3) or $[Ti(O\textit{i}\text{-}Pr)_4]_0$ (Entry 4 - 8) = 20 mM in toluene/alcohol (1/1 v/v) at 80 °C. [b] Measured by SEC. [c] Determined by ^{1}H NMR. [d] RMA: Monomer transesterified with the corresponding alcohol. [e] Glass transition temperature (T_g) and melting temperature (T_m) analyzed by DSC. [f] Polymerization at 40 °C. [g] Polymerization at 60 °C. [h] Polymerization in PEG-OH.

Conclusion

Sequence-controlled copolymers were successfully synthesized, in one-pot, by efficient, convenient, and versatile tandem catalysis combined with metal alkoxide/alcohol-mediated transesterification of methacrylates and ruthenium-catalyzed living radical polymerization of their monomers (Scheme 2). The concurrent tandem catalysis efficiently produces various gradient copolymers. The monomer sequence was controlled by species and/or concentrations of metal alkoxides and alcohols, and the reaction temperature. Monomer-selective or iterative transesterification gave random-gradient copolymers or gradient-block counterparts, respectively. This tandem catalysis can be applied to not only the synthesis of gradient copolymers but also that of random or block copolymers by controlling the initiation of transesterification and polymerization. This tandem catalytic system should open new aspects to prepare sequence-regulated copolymers.



Scheme 2. Sequence-Regulated Copolymers via Tandem Catalysis of Living Radical Polymerization and In-Situ Transesterification

Experimental Section

Materials

MMA (Tokyo Kasei, purity > 99.8%), methyl acrylate (MA; Tokyo Kasei, >99%), isopropyl methacrylate (*i*-PrMA: Tokyo Kasei, >98%), *tert*-butyl methacrylate (*t*-BuMA: Tokyo Kasei, >98%) and tetralin (1,2,3,4-tetrahydronaphthalene) (Kishida Chemical, >98%, internal standard for ^{1}H NMR analysis) were dried overnight over calcium chloride and distilled twice from calcium hydride under reduced pressure before use. Ethyl 2-chloro-2-phenylacetate (ECPA, Aldrich, >97%) was distilled under reduced pressure before use. Ru(Ind)Cl(PPh_3)$_2$ (Aldrich), Al(O*i*-Pr)$_3$ (Aldrich, >99%), Al_2O_3 (Aldrich, >99.99%), Fe_2O_3 (Aldrich, >99.98%) and Sb_2O_3 (Aldrich, >99.999%) were used as received and handled in a glove box under moisture- and oxygen-free argon (H_2O < 1 ppm; O_2 < 1 ppm). Ti(O*i*-Pr)$_4$ (Kanto Chemicals, >97%), $TiCl_4$ (Aldrich; 1.0 M in toluene), $SnCl_4$ (Aldrich; 1.0 M in toluene), BF_3OEt_2 (Aldrich) and $ZnCl_2$ (Aldrich; 1.0 M in Et_2O) were used as received. Ethanol (EtOH; Wako, dehydrated), 2-propanol (*i*-PrOH; Wako, dehydrated), benzyl alcohol (BzOH; Wako, >99%), 1-dodecanol (Dodecanol; Wako, >95%), poly(ethylene glycol) methyl ether (PEG-OH; Aldrich: M_n = 550), and *n*-Bu_3N (Tokyo Kasei, >99 %) were degassed before use. Toluene (solvent) was purified before use by passing through a purification column (Solvent Dispensing System; glass contour).

Transesterification

The reaction was carried out by the syringe technique under dry argon in baked glass tube equipped with a three-way stopcock. A typical procedure for Al(O*i*-Pr)$_3$ catalyzed transesterification of MMA with in toluene/EtOH (1/1, v/v) was done as below: Into a glass tube were added toluene (0.70 mL), Al(O*i*-Pr)$_3$ (0.48 mL of 125 mM in toluene, 0.06 mmol), MMA (0.64 mL, 6 mmol), and EtOH (1.18 mL) at room temperature under dry argon. The total volume of the reaction mixture was thus 3.0 mL. The glass tube was immediately placed in an oil bath kept at 80 °C. The reaction was followed by taking aliquots of the solution with a syringe under dry argon in predetermined intervals and then terminating by cooling to –78 °C. The conversion was determined by ^{1}H NMR in $CDCl_3$.

Gradient Copolymers via Tandem Catalysis

The polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock. A typical procedure is given below for tandem polymerization of MMA with ECPA/Ru(Ind)Cl(PPh_3)$_2$/Al(O*i*-Pr)$_3$ in toluene/EtOH (1/1, v/v): Into a glass tube with Ru(Ind)Cl(PPh_3)$_2$ (4.46 mg, 0.006 mmol) were added toluene (0.56 mL), tetralin (0.08 mL), Al(O*i*-Pr)$_3$ (0.48 mL of 125 mM in toluene, 0.06 mmol), MMA (0.64 mL, 6 mmol), EtOH (1.14 mL), and ECPA (0.1 mL of 610.0 mM in toluene, 0.06 mmol), sequentially in this order, at room temperature under dry argon. The total volume of the reaction mixture was thus 3.0 mL. The glass tube was immediately placed in an oil bath kept at 80 °C. The reaction was followed by taking aliquots of the solution with a syringe under dry argon in predetermined intervals and then terminating by cooling to –78 °C. Total monomer conversion and the monomer composition in a polymerization solution, and the repeat-unit composition of polymers were determined by ^{1}H NMR in $CDCl_3$ with tetralin as an internal standard. The quenched reaction solutions were washed with water and evaporated to dryness to give the products, which were subsequently vacuum-dried overnight. SEC ($CHCl_3$; PMMA std.): M_n = 11,300, M_w/M_n = 1.32. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.4-7.2 (5H, aromatic), 4.2 (2H, -CH(Ph)$CO_2C\boldsymbol{H_2}CH_3$), 4.1-3.9 (105H, -C($CH_3$)($CO_2C\boldsymbol{H_2}CH_3$)-), 3.7-3.4 (209H, -$CO_2C\boldsymbol{H_3}$), 3.35 (1H, -COC***H***(Ph)-), 2.1-1.4 (244H, -C$\boldsymbol{H_2}$-), 1.3-0.7 (527H, - CC$\boldsymbol{H_3}$).

Gradient Block Copolymers via Tandem Catalysis

The polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock as below: In an argon-filled glass tube was placed Ru(Ind)Cl(PPh_3)$_2$ (0.018 mmol, 13.97 mg), to which toluene (2.81 mL), tetralin (0.24 mL), Ti(O*i*-Pr)$_4$ (0.36 mL, as a 500 mM solution in toluene, 0.18 mmol), MMA (1.92 mL, 18 mmol), *i*-PrOH (3.42 mL) and ECPA (0.25 mL, as a 707.14 mM solution in toluene, 0.18 mmol) were added sequentially in this order at room temperature. The total volume of the reaction mixture was thus 9.0 mL. Immediately after mixing, the mixture was placed in an oil bath kept at 80 °C until the conversion reached around 50% (1st segment). The polymerization solution was partially (6.0 mL) transfer to the other baked glass tubes and then evaporated under reduced pressure under an inert and air-free atmosphere to remove the residual monomers and solvents, followed by the sequential addition of toluene (2.36 mL), MMA (1.28 mL, 12 mmol) and EtOH (2.36 mL), and the mixture was placed again in an oil

bath kept at 80 °C until the conversion reached around 50% (2nd segment). The same procedure with MMA and BzOH was conducted (3rd segment). In predetermined intervals at the each step, aliquots of the solution were sampled out and terminated by cooling to –78 °C to monitor the progress of the reaction. Total monomer conversion and the monomer composition in a polymerization solution, and the repeat-unit composition of polymers were determined by ^{1}H NMR in $CDCl_3$ with tetralin as an internal standard. The quenched reaction solutions were washed with water and evaporated to dryness to give the products, which were subsequently vacuum-dried overnight.

Measurements

The M_n, M_w/M_n, and MWD curves of the polymers were determined by size-exclusion chromatography (SEC) in chloroform at 40 °C using three polystyrene gel columns [Shodex K-805L (pore size: 20-1000 A; 8.0 mm i.d. × 30 cm) × 3; flow rate 1.0 mL/min] that were connected to a Jasco PU-980 precision pump, a Jasco RI-930 refractive index detector, and a Jasco UV/vis detector set at 250 nm. The columns were calibrated against 10 standard poly(MMA) samples (Polymer Laboratories; M_n = 630–1,200,000; M_w/M_n = 1.06–1.22). ^{1}H NMR spectra were recorded in $CDCl_3$ at room temperature on a JEOL JNM-LA500 spectrometer operating at 500.16 MHz. MALDI-TOF-MS analysis was performed on a Shimadzu AXIMA-CFR instrument equipped with 1.2 m linear flight tubes and a 337 nm nitrogen laser, with dithranol (1,8,9-anthracenetriol) as an ionizing matrix and sodium trifluoroacetate as a cationizing agent. Differential scanning calorimetry (DSC) was performed on polymer samples (ca. 4 mg weighed into an aluminum pan) under a dry nitrogen flow at a heating or cooling rate of 20 °C/min on a DSCQ200 calorimeter (TA Instruments) equipped with a RCS 90 electric freezing machine. Polymer samples for DSC and MALDI-TOF-MS analysis were fractionated beforehand by preparative SEC (column: Shodex K-5002 F).

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LIST OF PUBLICATIONS

Part I

Chapter 1

"Antithetic Function of Alcohol in Living Cationic Polymerization: From Terminator/Inhibitor to Useful Initiator"
Kazuhiro Nakatani, Makoto Ouchi, and Mitsuo Sawamoto
J. Polym. Sci., Part A: Polym. Chem. **2009**, *47*, 4194-4201.

Chapter 2

"Molecular Design of Counteranion in Alcohol-Initiated Living Cationic Polymerization toward Dual Control of Molecular Weight and Stereoregularity"
Kazuhiro Nakatani, Makoto Ouchi, and Mitsuo Sawamoto
to be submitted.

Part II

Chapter 3

"Terminal Umpolung in Metal-Catalyzed Living Radical Polymerization: Quantitative End-Capping of Carbon－Halogen Bond via a Modifier Monomer"
Kazuhiro Nakatani, Makoto Ouchi, and Mitsuo Sawamoto
Macromolecules **2008**, *41*, 4579-4581.

Chapter 4

"End-Functionalization with Alcohols in Metal-Catalyzed Living Radical Polymerization through Umpolung of Growing Carbon－Halogen Bond"
Kazuhiro Nakatani, Takaya Terashima, Makoto Ouchi, and Mitsuo Sawamoto
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Part III

Chapter 5

"Concurrent Tandem Living Radical Polymerization: Gradient Copolymers via In Situ Monomer Transformation with Alcohols"

Kazuhiro Nakatani, Takaya Terashima, and Mitsuo Sawamoto

J. Am. Chem. Soc. **2009**, *131*, 13600-13601.

Chapter 6

"Sequence-Regulated Copolymers via Tandem Catalysis of Living Radical Polymerization and Transesterification"

Kazuhiro Nakatani, Takaya Terashima, and Mitsuo Sawamoto

to be submitted.

Other Publication

"Ethanol-Mediated Living Radical Homo- and Copolymerization with Cp*-Ruthenium Catalysts: Active, Robust, and Universal for Functionalized Methacrylates"

Hiroaki Yoda, Kazuhiro Nakatani, Takaya Terashima, Makoto Ouchi, and Mitsuo Sawamoto

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